Chapter 1A: Biochemistry

Enzymes

The Kinetic Role of the Enzyme

1. The Two Laws of Thermodynamics:
    - #1: Energy cannot be created or destroyed (but it can be mutated)
    - #2: The disorder (entropy) of the universe tends to increase
2. Gibbs' free energy: $\Delta G = \Delta H - T\Delta S$
    - H = enthalpy, which is heat energy ($\Delta H = \Delta E - P\Delta V$)
    - T = temperature
    - S = entropy
3. Standard free energy change ($\Delta G_o'$) is ΔG with all reactants and products present at 1 M concentration, and pH = 7
    - $\Delta G^{o'} = -RT\ln K'_{eq}$ (K' is the ratio of reactants to products at equilibrium)
    - $\Delta G = \Delta G_o' + RT\ln K$ (so we can relate ΔG to $\Delta G_o'$)
        - K is the ratio of reactants to products at the time (not at equilibrium)
4. A catalyst lowers the activation energy (Ea) of a reaction without changing the ΔG
    - It lowers the Ea by stabilizing the transition state
    - It does not get consumed in the reaction
5. Check out an enzyme diagram:

Enzyme Structure and Function

6. Facts about enzymes:
    - Most of them are globular 3-D folded proteins (this allows for the specificity of the active site)
        - The active site is shaped such that the transition state of the reaction is stabilized
        - It is so specific shape-wise that it can even recognize different stereoisomers of a molecule
    - Proteases are enzymes which cleave proteins
        - Their active site usually has a serine because its OH group can act as a nucleophile to attack the carbonyl carbon of an amino acid to break the peptide bond
        - A recognition pocket is a site on the cleaving enzyme close to the active site which binds to specific amino acid residues in the substrate and allows the serine in the active site to cut at the right place
7. Ways to regulate enzyme activity:
    - Covalent modification (i.e. phosphorylation/dephosphorylation)
        - The phosphate is usually added to/removed from serine, threonine, or tyrosine
    - Proteolytic cleavage
        - The enzyme is called a zymogen before being activated to form an active enzyme (think GI tract)
    - Association with other polypeptides
        - Sometimes there can be regulatory subunits which bind to the enzyme and regulate it
    - Allosteric regulation
        - When different molecules bind to allosteric sites on the enzyme (think feedback regulation)

Basic Enzyme Kinetics

8. Saturation kinetics:

- Vmax = the reaction rate when the enzyme is saturated
- Km = the amount of substrate necessary to reach a reaction velocity of 0.5 Vmax

9. Cooperativity is when we have a multi-unit enzyme, and the binding of substrate to one subunit increases the affinity of other subunits for their substrates
    - This results in a sigmoidal reaction velocity graph because as more substrates are bound to enzyme, the velocity suddenly shoots up because affinity is increased
10. There are multiple ways to inhibit enzymes:
    - Competitive inhibition: compete with the substrate to bind at the active site
        - Vmax will stay the same
        - Km will increase
    - Non-competitive inhibition: the inhibitor binds to a site OTHER than the active site and renders the enzyme useless
        - Vmax decreases
        - Km stays the same

Other

11. **Know your amino acids (make chart elsewhere)**

<u>Enzymes and Cellular Respiration</u>

Energy Metabolism and the Definitions of Oxidation and Reduction

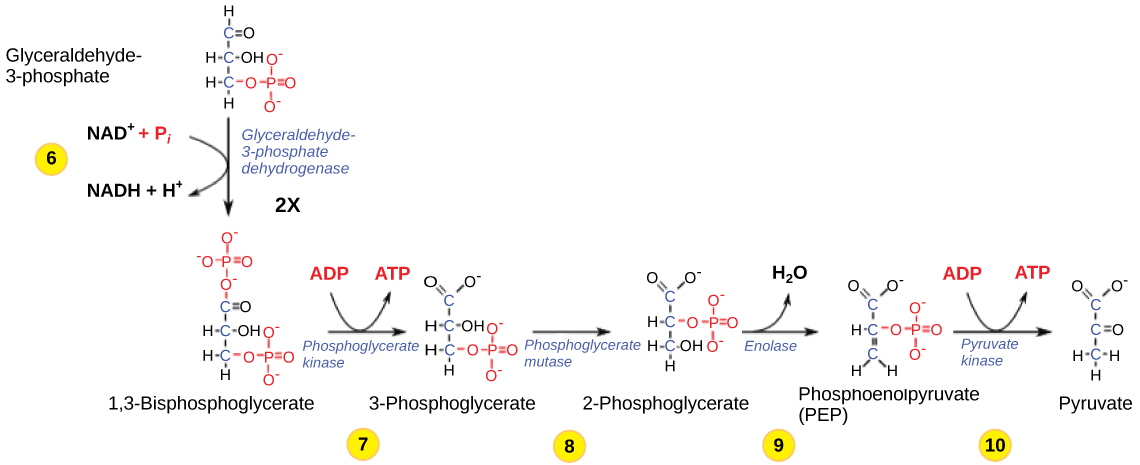
12. High-level energetics of life: energy is stored in reduced molecules like carbohydrates and fats, then they are oxidized to produce ATP and CO_2 (creating ATP is a non-spontaneous process so this is all one big coupled reaction)
13. Oxidation means:
    - Attach oxygen (or increase # of bonds to oxygen)
    - Remove hydrogen
    - Remove electrons
14. Reduction
    - Remove oxygen (or decrease # of bonds)
    - Add hydrogen
    - Add electrons

Introduction to Cellular Respiration

15. The 4 steps of cellular respiration are: glycolysis (cytoplasm), pyruvate dehydrogenase complex (PDC) (mitochondrial matrix), Krebs cycle (mitochondrial matrix), electron transport/oxidative phosphorylation (inner mitochondrial membrane)

Glycolysis

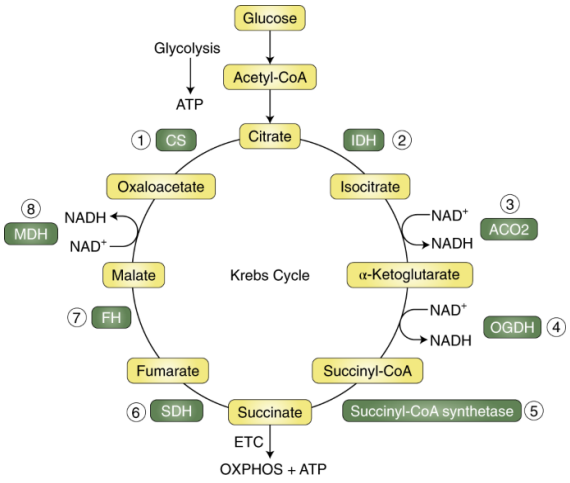
16. Refer to a glycolysis figure



17. Overall:
    - Take a glucose molecule (6 C's) and make it into 2 pyruvate molecules (3 C's each)
        - 2 ATP's used, 4 ATP's generated (per glucose, not per pyruvate)
        - 2 NADH's generated from NAD+'s
18. Note that:
    - Phosphofructokinase is a "committed" step because it uses ATP and is thus irreversible as well as because F-1,6-BP can only be used in glycolysis (no other pathways)
19. Fermentation:
    - This is not a "step" in cellular respiration unless it is an anaerobic environment, in which case something has to be done in order to regenerate the NADH which was formed from NAD+ during glycolysis
        - In yeast, the pyruvate is converted to ethanol
        - In animals, the pyruvate is converted to lactate
21. Overall: take the pyruvate from glycolysis (3 C's) and make it into an acetyl-CoA unit (2 C's), losing a CO2 in the process
    - Each pyruvate gives us 1 NADH, which means 2 NADH total per glucose
22. Note that:
    - The PDC is regulated by AMP levels: when they are high, it means that ATP is low and so the PDC is stimulated to action
    - The TPP is a non-protein molecule - a "prosthetic group" - which is part of the enzyme (attached to its active site)
        - As opposed to NAD+, which is a co-factor (necessary to the enzyme's function, but doesn't actually interact with it)

The Krebs Cycle

23. Look at a Krebs Cycle Figure



Overall: take the acetyl unit (2 C's), combine it with oxaloacetate (4 C's), then go through a cycle which will release 2 CO2's and create NADH, FADH2, GTP, etc.

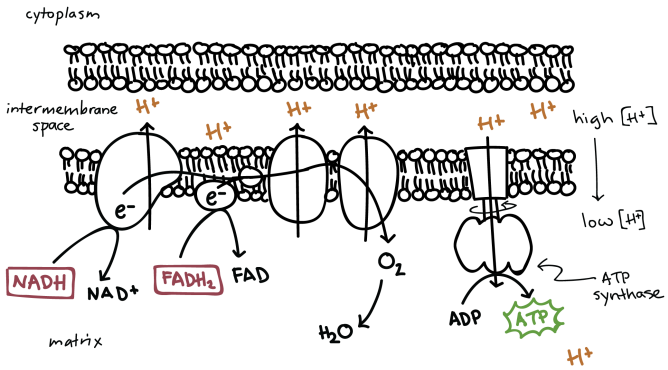
- Per glucose: 6 NADH, 2 FADH2, 2 GTP

Compartmentalization of Glucose Catabolism in Eukaryotes

25. The intermembrane space of the mitochondria is continuous with the cytoplasm of the cell because the outer mitochondrial membrane has large porins that let everything through
26. The inner membrane of the mitochondria is folded into "cristae", which allows for more membrane surface area
27. Prokaryotes do everything in the cytoplasm (no membrane-bound organelles) so they do not have to import the NADH produced in glycolysis into the mitochondria (this saves energy)

Electron Transport and Oxidative Phosphorylation

28. See figure:



29. Overall: every time the electrons get passed to a member of the ETC (i.e. that member is reduced), energy is released
30. Specifics:
    - 3 of the members are large proteins complexes with heme prosthetic groups or iron-sulfur electron-transfer systems
    - The 2 other members are smaller electron carriers that can actually move
    - The final member of the chain reduces oxygen to water (adds electrons and protons to oxygen)
31. Other names of the ETC members (make sure you understand why):
    - "A" also known as NADH dehydrogenase, coenzyme Q reductase
    - "B" also known as cytochrome C reductase
    - "C" also known as cytochrome C oxidase
32. You should be able to count up the total amount of ATP produced per glucose molecule using the following facts:
    - Each NADH molecule pumps 10 protons across the inner membrane as it goes through the ETC
    - Each FADH2 molecule pumps 6 protons (it enters at B)
    - The ATP synthase produces 1 ATP for every 4 protons
    - For eukaryotes, each NADH produced in glycolysis only produces 1.5 ATP (while bacteria produce 2.5)
        - This is because eukaryotes have to expend energy getting the NADH into the mitochondrial matrix

Chapter 1B

Chapter 1B: Gene Expression

<u>DNA and the Genetic Code</u>

DNA Structure

- The building blocks of DNA are deoxyribonucleoside 5' triphosphates (generally named dNTP's):
    - Ribose sugar without an oxygen
    - A string of 3 phosphates attached to the 5' carbon of the ribose
    - Aromatic base (adenine, guanine, thymine, or cytosin) attached to the 1' carbon of the ribose
        - A & G are purines (derived from purine) and have 2 carbon rings
        - C & T are pyrimidines (derived from pyrimidine) and have 1 carbon ring
    - OH group on the 3' carbon
- Nucleoside is just the ribose sugar and the aromatic base, while a nucleotide is a nucleoside + the phosphates

- Polynucleotide sequences are connected when the phosphate on the 5' carbon of one dNTP forms a phosphodiester bond to the 3' OH of another dNTP (this is where we get the 5'->3' direction from)
    - The phosphates are hydrolyzed in this process (energy releasing; spontaneous) so that there is only one phosphate bonded to the OH group, not a chain of 3
    - This means that pyrophosphate is a "leaving group", and when this subsequently gets hydrolyzed again, a lot of energy is released -- which is what drives the entire polymerization reaction forward

- DNA structure is a right-handed double helix held together by hydrogen bonds between complementary strands of DNA (understand every part of this statement…)
    - The 2 DNA strands are anti-parallel (5' vs. 3')
    - The H-bonds are always either between A and T or C and G (i.e. purine + pyrimidine…this is because the shapes of the molecules are conducive for H-bonding in that way)
    - Because the helix is coiled, we end up with the bases stacked on top of each other and this allows them to bond hydrophobically and have van der Waals reactions, which increases the molecule stability
- Binding 2 DNA strands together is called hybridization/annealing, and separating them is melting/denaturation
    - The temperature at which half of a solution of DNA is melted is called the Tm

- Difference between prokaryotes and eukaryotes:
    - Prokaryotes further stabilize their (circular!) genome by twisting the circle around on itself to form supercoils (it already has "regular" coils because of DNA's helix nature)
    - Eukaryotes stabilize their DNA by…
        - Wrapping it around globular proteins called histones (beads on a string)
            - "Bead" is a nucleosome - DNA wrapped around an octamer of histones
            - "String" between the beads is "linker" DNA
        - Then we pack the nucleosomes together to make chromatin

The Role of DNA

- Central Dogma of Molecular Biology:
    - DNA information is copied onto a complementary strand called mRNA
    - mRNA travels to the cytoplasm where the ribosome (with the help of rRNA and tRNA) take its information to make proteins

- There are many causes of genetic mutations (UV light, intercalation, mistakes in replication, etc.) but here are the 3 kinds of mutations:
    - Point mutations: single base pair substitution
        - Missense point mutations: cause one amino acid to replace another
        - Nonsense point mutations: cause a stop codon to replace a regular codon
        - Conservative missense point mutation: when the new amino acid is similar enough to the old one that the protein for all intents and purposes does not change much
        - Silent mutations: when the error does not change the amino acid being encoded or when it occurs in a part of the gene that does not encode for protein (i.e. introns)
    - Insertion mutations: adding nucleotides into the DNA sequences
        - This usually causes frameshift mutations, which is when the "reading frame" is thrown off and the ribosome does not "read" the mRNA in the correct sets of 3
    - Deletion mutations: removal of nucleotides from the sequence
        - This can also cause frameshift mutations

DNA Replication

- DNA replication is semi-conservative, which means that when you take a double-stranded DNA helix apart and copy it, you make 2 new double-strands…and one strand in each of the double-strand is from the "parent" DNA helix
- Polymerization (catalyzed by DNA polymerase) is the process of adding new dNTP's (nucleotides) to a nascent DNA chain
    - It is ALWAYS in the 5'->3' direction

- DNA polymerase requires a template (thus it is more appropriately called DNA-dependent DNA polymerase)
    - Thus the template is READ in the 3'->5' direction, since the resulting combination of new and old strands must be anti-parallel
- DNA polymerase requires a primer (it cannot start a new DNA chain on its own)
    - An RNA polymerase enzyme called primase does the priming, filling it in with RNA nucleotides which are later replaced by DNA

- In order to start DNA replication, we have to unwind the double helix and then separate the "annealed" strands
    - Helicase does BOTH of these jobs
        - It starts at a specific location called the origin of replication
    - Because unwinding the strand at one location will cause it to wind more tightly at another location, we relieve the pressure by using topoisomerase enzymes to cut and re-wind the DNA
    - The unwound single DNA strands are not very stable on their own, so we stabilize them with single-strand binding proteins

- One problem is that as replication proceeds to either side of the origin of replication, think about the replication forks that are created…only one half of the fork can be traveled on in a 3'->5' direction, which is how we need to be reading the template
    - Thus we have leading and lagging strands, where the lagging strand is actually made up of many smaller "Okazaki fragments" which are created in a 5'->3' direction
        - The fragments are later joined up by DNA ligase, another enzyme

- Eukaryotic vs. Prokaryotic Replication:
    - Eukaryotic replication: we have many different replication bubbles, which means that on a particular chromosome, there are many different origins of replication
    - Prokaryotic replication: it is called "theta" replication
        - Remember it is a circular genome…we start at only ONE origin of replication, and as it proceeds to both sides the genome starts to look like the θ symbol

- In more detail: prokaryotic DNA polymerase
    - There are actually 3 different kinds of DNA polymerase: I, II, and III
        - DNA polymerase I removes the primer and replaces it with DNA
            - It has 5'->3' exonuclease activity, which means that it traverses the primer in the 5'->3' direction, removing nucleotides as it goes
        - DNA polymerase II is unknown
        - DNA polymerase III does the main job of elongating the leading strand
            - It can go backwards for short times to fix mistakes: this is called 3'->5' exonuclease activity

<u>Gene Expression</u>

RNA and Transcription

- RNA is different from DNA in the following ways:
    - It is (normally) single-stranded
    - It has all the same bases as DNA except it uses uracil (U) instead of thymine (T)
    - The ribose sugar is not deoxy, meaning that on the 2' carbon there is an OH group
        - This group makes RNA less stable (can mutate more) because the OH group is close enough to the phosphate to attack it and in so doing break up an RNA polymer

- Prokaryote vs. eukaryote

- Prokaryotes are "polycistronic", which means that a single mRNA strand codes for more than one polypeptide (not because of different reading frames but because they are one after another)
    - Although the proteins are usually related in function

Transcription

- Once again we are doing polymerization/chain elongation, except this time it is using RNA polymerase (no primer needed) instead of DNA polymerase
    - RNA polymerase does not have 3'->5' exonuclease activity, so transcription is not as reliable as replication
- More differences from replication:
    - Instead of the origin of replication we have the "start site" (and it only goes in one direction)
        - The sequence of nucleotides immediately before the start site is called the "promoter", and this is where RNA polymerase goes first to get activated
    - Only one of the DNA strands is going to get transcribed to RNA, and it is called the template/non-coding/transcribed/anti-sense strand
        - The other strand is called the coding/sense strand, because the nucleotides it holds are the ones which will actually be used (remember because the mRNA which gets transcribed is complementary to the anti-sense strand, just as the sense strand is)

- Comparing prokaryotic and eukaryotic transcription:
    - Location of transcription
        - Prokaryotes do it free in the cytoplasm
        - Eukaryotes make mRNA in the nucleus then transport it outside into the cytoplasm
    - Primary transcript and mRNA
        - Prokaryotes' primary transcript (i.e. the mRNA that comes straight off the transcription process) is ready to be translated right away (actually, since everything happens in the cytoplasm, translation starts on a chain of mRNA even before its transcription is complete!)
        - Eukaryotes' primary transcript is NOT ready to go - it is modified extensively before translation:
            - Splicing (remove the stuff, called introns, that don't code for proteins like regulatory sequences…and just have the "exons", or the part that actually codes for protein)
                - The RNA transcript BEFORE splicing occurs is called heterogeneous nuclear RNA (hnRNA)
            - Add 5' cap to help with translation
            - Attach 3' poly-A tail to protect against exonucleases
    - RNA polymerase(s)
        - There are 3 different kinds of RNA polymerases for eukaryotes (note that this is flipped from before, when PROKARYOTES were the ones with 3 DNA polymerases):
            - RNA polymerase I (transcribe rRNA)
            - RNA polymerase II (transcribe mRNA)
            - RNA polymerase III (transcribe tRNA)
    - Regulation of transcription
        - It's just generally more complex in eukaryotes than in prokaryotes…eukaryotes have sequence-specific transcription factors, TAT boxes, etc.

Translation

- The important structure here is transfer RNA (tRNA), which has a site called an "anticodon" to bind to the mRNA and an "amino acid acceptor" site
    - Attaching the amino acid to the tRNA requires hydrolyzing one ATP…so first we get aminoacyl AMP
    - And then we attach that to the tRNA ("tRNA loading"/"amino acid activation"), which is unfavorable but driven forward by taking off the AMP
    - And at the end, we have aminoacyl tRNA
        - The amino acid-tRNA bond is ALSO high energy, and so when we break it to attach the amino acid to the polypeptide chain, we can use that energy to drive the reaction forward
    - The whole "match amino acid with tRNA" process is handled by aminoacyl-tRNA synthetases

- Ribosome stuff…
    - It's basically this big huge mass of polypeptides and mRNA
    - There are two subunits: large and small
    - When the subunits are attached together, the ribosome is good to go and there are 3 binding sites:
        - P site (peptidyl-tRNA), i.e. where the growing polypeptide chain while still attached to tRNA is located in translation
        - A site (aminoacyl-tRNA), i.e. acceptor site - where each new tRNA delivers its amino acid

- Prokaryotic translation
    - Firstly remember that translation starts even when transcription is still going
        - Also know that MULTIPLE ribosomes work on the same mRNA at once - this is called a polyribosome
    - Initiation:
        - Translation does not begin at the 5' end of the mRNA…it's just a bit further down the chain…
            - First there is a "promoter" called the "ribosome binding site" aka "Shine Dalgarno sequence", and then the actual start codon
        - To actually start initiation we have to put together the ribosome, so we do: small subunit + initiation factors + mRNA + large subunit (in that order) **(cost one GTP)**
        - Then we attach the first aminoacyl-tRNA complex to the start codon, which sits in the P site
            - The amino acid is always formyl-methionine (a modified methionine)
    - Elongation:
        - The next aminoacyl-tRNA enters the A site **(cost one GTP)**
        - Then "peptidyl transferase" activity causes the P site amino acid to peptide bond with this new amino acid
        - Then translocation: the new tRNA + new amino acid moves into the P site **(cost one GTP)**
        - So you will notice that translation of the polypeptide goes from N-terminus to C-terminus
    - Termination:
        - When a stop codon appears in the A site, we get a "release factor" instead of tRNA in the A site, which causes peptidyl transferase to hydrolyze the bond between the last tRNA and the completed polypeptide
        - The ribosome separates into subunits and we're good to go

- Differences in eukaryotic translation (there are just a few):

- The ribosome is 80S instead of 70S
- mRNA is processed after transcription, before translation starts
- The N-terminal amino acid is plain methionine, instead of fMet (formyl methionine)

Chapter 2

Chapter 2: Microbiology

Viruses

Viral Structure and Function

- Stuff about viruses:
  - Viruses are infectious agents that attack all life forms (plants, animals, protists, and bacteria)
  - They are "obligate intracellular parasites", which means…
    - Obligate: they HAVE to be intracellular (if they are outside the cell, they can do no harm)
    - Intra: as intimated above, they have to be inside
    - Parasite: they "feed off" the cell's mechanisms - they cannot survive on their own
  - They rely on "host machinery" as much as possible, which means that they use the cell's ability to translate DNA/RNA, make proteins, etc.
  - They are SPECIFIC - they only attack certain cells - the ones which have receptors on their surface which match the virus' shape
- Structure of viruses:
  - All viruses have a nucleic acid genome packaged in a protein shell
    - The genome can be either:
      - DNA or RNA
      - Single or double-stranded
      - Linear or circular
    - The nucleic acid of a virus is ONLY its genome and nothing else (as opposed to regular cells which have non-genomic nucleic acid material, such as mRNA, tRNA, etc.)
    - The protein coat is called the "capsid", and we classify viruses based on the shape of the capsid (i.e. its morphology):
      - Helical capsids are rod-shaped
      - Polyhedral capsids are multiple-sided geometric surfaces
    - Surrounding the capsid there is an "envelope" - the virus gets this from the membrane of the HOST CELL…
      - It contains:
        - Phospholipids, proteins, and carbohydrates from the host membrane
        - Proteins encoded by the viral genome itself
      - A virus acquires its envelope by budding through the host membrane
  - They are SMALL (much smaller than the host cells they infect)
    - The protein packaging for the genome is rigid, so it cannot accommodate "expansion"
    - The virus deals with this by being efficient (again by using host machinery whenever possible, and also by using multiple reading frames so that a single strand of DNA/RNA can encode more than one protein sequence)

Bacteriophage Life Cycles

- The first part:
    - First the viruses binds to the exterior of a bacterial cell (so we are focusing on bacteria here, as shown by the title "bacteriophage" life cycles) - and this is called "attachment" or "adsorption"
    - Then the viral genome (but not the envelope or the capsid!) is injected into the host cell
    - Then we go into the lytic cycle OR the lysogenic cycle
- Lytic cycle (this one goes bang bang bang):
    - Once the genome is in, it gets transcribed/translated right away by the host cell's polymerases and ribosomes
        - One of the first gene products is hydrolase, which destroys the ORIGINAL genome (i.e. the genome of the host…we don't need that anymore!)
    - Then we have DNA/RNA replication to make multiple copies of the virus' genome, using the nucleotide bases which are the result of the hydrolysis of the host genome
    - Capsid proteins are also made for all these new viral genomes, so they can become real viruses
    - Finally we get an enzyme called lysozyme, which destroys the bacterial cell wall
        - Now the cell MEMBRANE still remains, but because the cell wall is destroyed, osmotic pressure causes the cell to lyse, and all those new viruses come out
- Lysogenic cycle (coming in all quiet-like):
    - The idea here is that the virus doesn't destroy the host cell right away, like it does in the lytic cycle…when it enters the cell, it just incorporates itself into the host genome and DOES NOT GET EXPRESSED (transcription is blocked by a repressor protein)
        - At this point the viral genome is called a prophage
    - But the thing is, now every time that host cell reproduces itself, the virus will reproduce as well
    - And then at a certain point…EXCISION happens, which is when the viral genome excises itself from the host genome and is now loose and free in the bacterial cell - and then the lytic cycle starts
        - Sometimes when it excises itself, it takes some of the host cell's genome along with it and this gives it a new feature (i.e. the virus suddenly codes for a protein which metabolizes galactose) - this is called transduction
- Differences for animal viruses (as opposed to bacteriophages aka bacteria-invading viruses):
    - The receptors on the cell surface which the virus binds to are not JUST for the virus - they are involved in the cell's regular function as well
    - When viruses enter animal cells, it's not by "injection" - it is usually by endocytosis (which is not possible with bacteriophages because of the cell wall)
        - This means that the virus has to be uncoated after it enters the cell, because unlike bacteriophages they do NOT leave their capsid outside during the penetration process
    - Differences in cycles:
        - Lytic cycle the same
        - There is a new one called the productive cycle: it is the same as the lytic cycle, but it does not destroy the host cell because the viruses exit the cell by "budding" through the membrane (this is how they coat themselves with the membrane as well)
        - Lysogenic cycle the same, except it is called a "provirus" instead of a prophage

Viral Genomes

- Let's think about what kind of proteins a virus must encode or carry based on its genome type:
    - (+) RNA viruses (i.e. a piece of single-stranded viral RNA which serves as mRNA):
        - OK obviously we can do translation right away because it will serve as mRNA, so all we need to worry about is how to replicate the RNA so that more viruses

can be made…so we need RNA-dependent RNA polymerase (but we don't have to HAVE it with us…we can just encode it, then let the ribosomes make it)

- (-) RNA viruses (i.e. a piece of single-stranded RNA that is complementary to the actual viral RNA):
    - Here we can't do translation right away - we have to make the real strand first from the complementary strand, so it must CARRY RNA-dependent RNA polymerase
- Retroviruses (i.e. (+) RNA viruses which undergo lysogeny, which means they incorporate into the host genome):
    - The problem with lysogeny is that the virus needs to become double-stranded DNA in order to fit into the host genome, meaning that they need to undergo the process called "reverse transcription" - an enzyme called RNA-dependent DNA polymerase can do this
    - But they only have to ENCODE the enzyme, because when the RNA gets into the cell it can get translated by the ribosome right away
- Double-stranded DNA viruses:
    - These boys encode enzymes required for dNTP synthesis and DNA replication…even though yes, the host cell will have these enzymes too. The issue is that the host cell will only create those dNTP's and replicate the DNA when it is time for the cell ITSELF to replicate…thus the virus needs to bring its own crap if it wants to go by its own time table

<u>Prokaryotes</u>

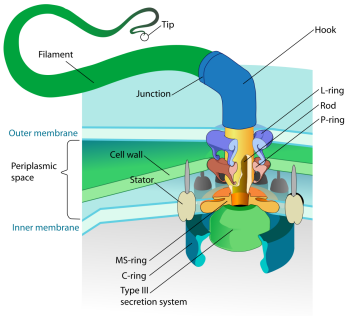
Introduction

- The main difference between prokaryotes and eukaryotes is that prokaryotes do not have a nucleus or any other membrane-bound organelle, for that matter (however they can still carry out all the same life processes as a eukaryote can)
- Living organisms in general are classified using many levels…the highest is kingdom, and there are 5: prokaryotes, single-celled eukaryotes, fungi, plants, and animals

Bacterial Structure and Classification

- So we are talking about the bacterial cell…i.e. a prokaryote…
- Contents of the cytoplasm:
    - Recall there are no membrane-bound organelles
    - The genome is a double-stranded CIRCULAR DNA chromosome (no nucleus/histones)
        - Transcription and translation happen in the same place, at the same time
        - Bacterial ribosomes are structurally different than eukaryotic ones, although they do the same thing (this allows us to make drugs that target only bacterial ribosomes)
    - There is also a plasmid, which is genetic material but NOT part of the genome…it is just off by itself…an "extrachromosomal genetic element"
        - The plasmid encodes gene products that give an advantage to the cell, and also orchestrate exchange of genetic information between bacteria (conjugation)
- Cell membrane/cell wall:
    - There is a cell wall (prevents osmotic pressure-related problems) and a cell membrane
        - The cell wall is composed of peptidoglycan - a combination of amino acids and sugars that is unique to prokaryotes
        - This cell wall is usually what anti-biotics target, because if they can break it, then the cell will burst due to osmosis
    - Gram staining of the cell wall:
        - Bacteria can also be classified based on the result of a Gram staining of the cell wall: Gram-negative bacteria stain weakly and Gram-positive bacteria stain strongly

        - Gram-negative bacteria have a (relatively) thin layer of peptidoglycan in their cell wall (it is this stuff that gets stained), but then also an ADDITIONAL layer outside that made of lipopolysaccharides that provides additional protection
            - Between the 2 layers is the "periplasmic space", where we have enzymes that kill anti-biotics (so gram-negative bacteria is really good against anti-biotics not only because it has more layers of protection but also because it has a double layer)
        - Gram-positive bacteria just have the cell wall, which has a really thick layer of peptidoglycan in it
    - Endotoxins vs. exotoxins:
        - Endotoxins are a normal part of the outside layer of Gram-negative bacteria…but they can be bad if a lot of bacteria die and their outer membranes disintegrate and release these endotoxins
            - The body's immune system responds by releasing tons of chemicals, which causes the body to go into septic shock (blood enters the tissues, blood pressure drops, etc.)
        - Exotoxins are always bad - they are toxic substances released by both Gram-negative and Gram-positive bacteria that kill other bacteria so that the releasing bacteria can have a chance to live
- Capsule/glycocalyx:
    - It's just a sticky layer of polysaccharide that surrounds the bacterial cell (sometimes around a whole bacterial colony)
    - It makes the bacteria hard for the immune system to get to, and also allows the bacteria to stick to smooth surfaces
- Flagella:
    - This is just a long, whip-like filament which bacteria can use to get around (at the cost of ATP)
    - It breaks down to:
        - Filament
        - Hook
        - Basal structure (anchor the flagellum to the outside of the bacterial cell and rotates the rod and the rest of the flagellum as necessary)
    - See figure:



    - The flagella moves the bacteria according to a process called chemotaxis, where the bacteria figures out which direction to go in for food by using chemoreceptors to detect changing concentrations of some substance
- Pili:

- This is a long projection on the bacterial surface which is involved in attaching to different surfaces
- We also have the fimbriae, which are smaller and do the same thing

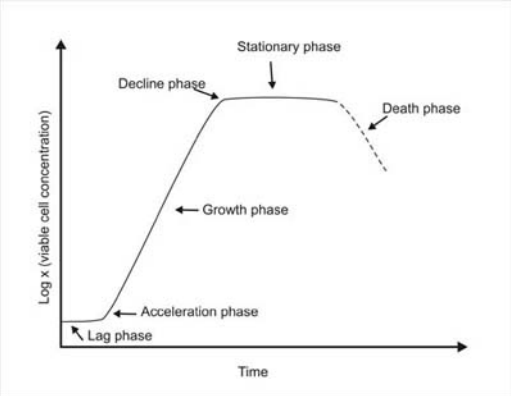
Bacterial Growth Requirements and Classification

- Different terms:
  - Medium: is the environment where the bacteria grow (but this is NOT their food)
    - Most common medium is agar, based on seaweed
  - Plating: putting bacteria onto a dish with some sort of medium to see if they will grow
  - Colony: a crop of bacteria which have grown in some place
  - Minimal medium: agar plus only glucose (to feed the bacteria)
  - Wild-type bacteria: a type of bacteria which has ALL the characteristics that are natural for that particular species
  - Plaque: "clear" spot amongst a colony (or a "lawn", when growth is dense) where bacteria have died
- Classifying bacteria by how they eat:
  - We sub-classify based on carbon source and energy source:
    - Autotrophs use CO2 as their carbon source
    - Heterotrophs rely on organic nutrients created by other organisms (i.e. glucose)
    - Chemotrophs get their energy from chemicals
    - Phototrophs get their energy from light
  - So we can combine these terms to have "chemoautotroph", "photoautotroph", etc.
  - The last important type is "auxotroph", where the bacteria needs something beyond carbon/energy to live, i.e. "arginine auxotroph" where the bacteria needs to get arginine from somewhere since it can't make it on its own
- Classify based on temperature:
  - Each bacteria grows optimally or maybe even can only survive at certain temperatures…
    - Mesophiles: moderate temperatures (around 30 Celsius)
    - Thermophiles: very hot (up to 100 Celsius)
    - Psychrophiles: cold (around 0 Celsius)
- Classify based on oxygen utilization and tolerance:
  - Bacteria which require oxygen to do metabolism (i.e. cannot do anything in its absence): obligate aerobes
  - Bacteria who don't require oxygen (but might still used it): anaerobes
    - Facultative anaerobes: use oxygen when available, but don't NEED it to survive
    - Tolerant anaerobes: never use oxygen but can grow in its presence
    - Obligate anaerobes: don't use oxygen and are in fact poisonous
  - Some bacteria do anaerobic respiration, which is when bacteria do cell respiration but with the external electron receptor being something OTHER than oxygen (i.e. nitrate, carbon dioxide, sulfur oxide)
- Classify based on shape:
  - See table:

Bacterial Life Cycle

- Bacteria produce asexually: each cell just produces double the cellular components, then replicates the genome, then splits (no meiosis, recombination, etc.)
  - This means that genetic diversity is never introduced into bacteria via reproduction

- Bacterial growth figure:



-
    - Bacterial growth (in ideal conditions) is exponential (so the log of the population count grows linearly with time)
    - However, before getting into "exponential growth mode" aka the "log phase", there is a "lag phase" where cell division does not occur (this is because the bacteria have to make all the cellular components needed for division)
    - Then at the end, there is a "stationary phase" where they don't grow anymore because there aren't any more nutrients
- Sometimes bacteria form "endospores", which is like hibernation when conditions for growth are bad
    - This means they get tough, thick external shells made of peptidoglycan
    - They can survive very hot temperatures, so if we want to clean something completely we have to make it very high temperature
    - The metabolic reactivation of endospores is called "germination"

Genetic Exchange Between Bacteria

<u>Fungi</u>
Fungal Structure
Fungal Life Cycles

<u>Advanced Topic: Recombinant DNA</u>

[Chapter 2 Addendum]

Genetic Exchange Between Bacteria

- OK first let's realize that there are 3 ways that bacteria do "mutate" or at least acquire new genetic material (remember that reproduction is not going to be one of these, since they reproduce asexually):
    - Transduction (remember how the lysogenic cycle works)
    - Transformation (it's a bit weird, but pretty much you dump bacteria into a culture then add pure DNA, then the bacteria will take up the DNA)
    - Conjugation (OK, this is the most common one…let's talk about this)

- The high-level concept of conjugation is that bacterial cells touch each other physically and then transfer genetic information

- The genetic information normally transferred is known as the "F" factor, which is "extrachromosal DNA" in that it is not part of the normal bacterial circular chromosome
- The way this works is that there male and female bacterial cells
  - Male cells are "F+", meaning that they have the F factor
  - Female cells are "F-", meaning that they receive the F factor from the male (although the F factor is copied, so the original male cell remains male)
- So you can see that the "F" factor - thus the genes which are on it - is definitely going to be a part of the "new" genetic material received by a bacterial cell
  - There is also, however, another situation in which even more information is transferred
  - This is a situation in which the F factor is actually integrated into the MAIN GENOME of the bacterial cell
  - So what does this mean? It means that when the cell is copying the F factor in preparation for transfer to the female cell, some of the original genome gets copied along with it and so the female cell gets even more than it bargained for
  - These cells are called Hfr or "high frequency of recombination" cells

<u>Fungi</u>

Fungal Structure

- OK so now we're talking about fungi. Remember that they are the 3rd kingdom that we really get into during this course…the others being prokaryotes (of which bacteria is one) and animals
- So the fungi is its own kingdom…but at a higher level, it is just a multi-celled eukaryote

- OK, some quick shots:
  - Fungi have a cell wall made from chitin (different material than plant and bacterial cell walls)
  - All fungi are chemoheterotrophs
    - Recall "chemo" means that they get energy from chemicals rather than the sun (photo)
    - Recall "hetero" means that they use organic materials from other organisms as their carbon source, unlike autotrophs which use CO2
  - Most fungi are obligate aerobes (means that they must be in an oxygen-rich environment)

- The hierarchy for fungi structure is as follows
  - Cell (of course)
  - Hypha (long filament of cells joined end to end), of which there are 2 kinds
    - Septate hyphae have the cells separated by walls
    - Aseptate hyphae have NO separation, meaning that the cytoplasmic contents and nuclei are shared amongst all the cells
  - Mycelium (a meshwork of hyphae)
  - Thallus (many mycelium, which result in a structure visible to the naked eye)

Fungal Life Cycles

- OK, let's first realize that fungi reproduce both sexually and asexually

- Let's talk about asexual reproduction
  - This occurs by budding, fragmentation, or spore production
    - Budding: a new smaller cell grows outward from an existing one
    - Fragmentation: the mycelium is broken into small pieces which then grow into their own myceliums
    - Spore production: many spores form from one cell

        - Recall from the concept of the bacterial spore that the fungal spore has a tough wall resistant to environmental extremes
    - THE MAIN POINT: since it is ASEXUAL, the resulting "offspring" will always be identical genetic clones of the original cell

- Let's talk about sexual reproduction
    - The one point to understand for sexual reproduction is that all fungi are HAPLOID, which is opposite to the diploid cells that humans have
        - Haploid means that they only have one copy of each kind of chromosome
    - So when the fungi reproduce sexually, what happens is that two haploids combine together to make a diploid, but then they separate to more haploids
        - When they are in the diploid stage, chromosome may (ostensibly) get switched around so that when they split to make haploids again, there is new genetic material
        - And so these haploids just undergo mitosis to make more of themselves

Chapter 3

Chapter 3: Generalized Eukaryotic Cells

<u>Part 1: The Organelles</u>

- Quick overview of organelles in the cell and the number of membranes they have surrounding them:
    - Nucleus (2): contain and protect DNA, transcription, partial assembly of ribosomes
    - Mitochondria (2): produce ATP
    - Ribosomes (0): synthesize proteins
    - RER (1): synthesis and modification of secretory, membrane-bound, and organelle proteins
    - SER (1): detoxification and glycogen breakdown in liver; steroid synthesis in gonads
    - Golgi (1): modification and sorting of protein, some synthesis
    - Lysosomes (1): contain acid hydrolases that digest various substances
    - Peroxisomes (1): metabolize lipids and toxins using H2O2

The Nucleus

- The genomic material (DNA) is organized into chromosomes
    - Each chromosome has a "centromere" in the middle to help with mitosis and meiosis
        - They also have telomeres at the ends (large numbers of repeated DNA sequences) which help to protect the chromosome from degradation
    - Some parts of the chromosome are organized into regions called "heterochromatin", which are tightly packed and the genes are inaccessible
        - But other regions called euchromatin are more loosely packed and here the genes are active
- The nucleus is supported by a cytoskeleton-analog called "nuclear matrix" or "nuclear scaffold"

- The nucleolus is a region within the nucleus that makes ribosomes, so it has DNA, RNA polymerases, rRNA, and the protein components of the ribosome
    - The ribosome is PARTIALLY assembled here by the nucleolus - the rRNA is transcribed and the ribosomal subunits are attached, and then it is sent out into the cytoplasm so that translation (remember all translation happens in the cytoplasm) can happen and we add the necessary proteins

        - This also helps to prevent the translation of hnRNA, which could happen if we had fully functioning ribosomes in the nucleus

- The nuclear envelope is the "membrane" that surrounds the nucleus - in fact it is 2 lipid bilayer membranes
    - At some points, the inter-membrane space is continuous with the lumen of the endoplasmic reticulum
    - The envelope also has "nuclear pores" that allow small items to diffuse into the nucleus from the cytoplasm
        - Bigger items are only allowed in if they have a "nuclear localization sequence"

Mitochondria

- Mitochondria have their own mini-genome - it is a circular DNA molecule
    - They have their own way of doing everything - DNA replication, translation, ribosomes, etc.
    - It is only passed from the mother to the children ("maternal inheritance")
- The endosymbiotic theory of mitochondrial evolution suggests that the mitochondria was once an independent unicellular organism living within larger cells
    - This is because it can do all this stuff - make its own DNA, etc.

Endoplasmic Reticulum

- The ER is basically just a large system of folded membrane
- There are 2 types:
    - The rough ER has ribosomes bound to its surface, thus it is the site of protein synthesis for proteins targeted to enter the secretory pathway
    - The smooth ER doesn't make proteins…but it contains enzymes for steroid hormone synthesis or in the degradation of environmental toxins

- More on the secretory pathway:
    - OK so there are two sites for translation in the cell: on the rough ER and on ribosomes which are just free in the cytoplasm
    - Basically, any protein synthesized on the rough ER will end up either: secreted into the extracellular environment, as an integral plasma membrane protein, and in the membrane OR interior of the ER, Golgi, or lysosomes
        - The way the proteins get to and from all these compartments is by traveling in vesicles (so in a sense we COULD say that they are all contiguous)

- Every protein has an amino acid sequence that determines WHERE it will get translated
    - So the idea is that it binds to any random ribosome first and starts translating…but once the sequence has been attached, the "signal recognition particle (SRP)" binds to the whole ribosome and now we have a ribosome-SRP complex that binds to the rough ER
        - And then from there, as the protein is translated it goes into the rough ER (where a signal peptidase cuts off the unnecessary part)

- Integral membrane proteins are different - these also have "signal sequences" that cause their translation to be localized to the ER membrane, but there are a few differences:
    - As translation is happening, the hydrophobic transmembrane domains are threaded through the ER lumen
    - After translation is complete, the "signal sequences" are NOT cleaved off

- The rough ER also does glycosylation and disulfide bond formation for proteins

The Golgi Complex

- It is a group of membranous sacs stacked together like collapsed basketballs
- It has the following functions:
    - Modification of proteins made in the rough ER
    - Sorting and sending proteins to their correct destinations
    - Synthesizing macromolecules (i.e. polysaccharides) to be secreted

- The Golgi is divided into cis, medial, and trans
    - The protein-containing vesicles coming off the ER go to the cis stack and eventually exit at the trans stack in a specific direction (as determined by the Golgi in concert with special signals on the protein itself)
    - To be more specific, once a protein leaves the Golgi, there are 2 secretory pathways it can go on:
        - Constitutive secretory pathway: it goes directly to the cell surface and exits no matter what
        - Regulated secretory pathway: they stay in their secretory vesicles but don't actually exit until they get signaled to

Lysosomes

- They do both autophagy (self-eating, when intracellular components are messed up) and they participate in phagocytosis (when the cell engulfs something from the outside world and it is now inside the cell to be broken down) and lastly crinophagy (digesting unneeded excess secretory products)
- The enzymes which digest stuff are called acid hydrolases, because they only work in acidic environments

Peroxisomes

- They are called peroxisomes because hydrogen peroxide is a by-product of the metabolic reactions they perform, which include:
    - Lippid breakdown
    - Detoxification of drugs in the liver
- Even though hydrogen peroxide is damaging, this is not an issue because peroxisomes also have an enzyme called catalase that converts H_2O_2 -> $H_2O + O_2$

<u>Part 2: Structural Elements of the Animal Cell</u>

Membranes of the Eukaryotic Cell

- The membrane includes: phospholipids, glycolipids, and cholesterol
    - Phospholipids are glycerol attached to two fatty acids and a phosphoryl group (maybe phosphoryl choline)
    - Glycolipids have fatty acids but then carbohydrate side chains
- Fatty acids form micelles, but phospholipids form bilayer membranes (due to steric hindrance)

- Proteins are part of the membrane; they perform many different functions
    - Some are cell-surface receptors, which sit on the outside of the bilayer and bind signal molecules that come along, such as hormones, then relay this message into the cell
    - Others are channel proteins, which selectively allow ions or molecules to cross the membrane
- Another way to classify proteins is integral (goes through the entire membrane and thus has portions in the membrane and portions out of the membrane) or peripheral (purely on one side of the membrane or the other - attached to integral membrane proteins)
    - Remember that proteins get embedded in the membrane as they are made in the rough ER - and then the vesicle comes and "fuses" with the membrane

- The membrane can be described with a "fluid mosaic model", where things can move laterally but not up and down (due to hydrophilic/hydrophobic repulsion)

- The fluidity of a membrane is affected by what kind of lipids are in there
    - Saturated fatty acids on the phospholipids mean they are straighter and thus easier to pack together - this means we are LESS FLUID because the phospholipids are closer together
    - Cholesterol fits itself in between the lipids and breaks up the continuity (thus making it MORE FLUID)

Passive Transmembrane Transport

- Facilitated diffusion happens with: channel proteins and carrier proteins
    - Channel proteins are just a protein with an opening that the ion can travel through
        - Sometimes they are "voltage gated" or "ligand gated", which means that they can open and close in response to voltage changes or ligand binding
    - Carrier proteins (ALSO transmembrane) don't have a tunnel, but they have it so that the ion binds to the protein on one side of the membrane, then the protein undergoes a conformational change so that the molecule moves to the other side of the membrane
        - There are different kinds of carrier proteins:
            - Uniports (transport one molecule at a time)
            - Symports (carry two molecules in the same direction)
            - Antiports (carry two molecules in opposite directions)

- There are also other things called pores where they are big enough that they are NOT selective in what they allow to pass
    - These things are made by polypeptides called porins

Active Transport

- In active transport, molecules are moved against a gradient (not always concentration - it could be electrochemical as well)
    - Primary active transport is coupled with ATP hydrolysis
    - Secondary active transport is coupled to the flow of some other ion DOWN its electrochemical/concentration gradient (this is different from the antiport in facilitated diffusion because there we have both ions moving DOWN their concentration gradients)

The Na/K ATPase and the Resting Membrane Potential

- 3 Na+ out, 2 K+ in
    - But the thing is, K ions leak back OUT through potassium leak channels, which means we end up with an overall positive charge outside the membrane

- The roles of the Na/K ATPase are:
    - Maintain osmotic balance
    - Establish the resting membrane potential
    - Provide the sodium concentration gradient for driving secondary active transport

Endocytosis and Exocytosis

- Endocytosis is when the cell membrane invaginates to form a vesicle called an "endosome"
- There are 3 kinds of endocytosis:
    - Phagocytosis: non-specific uptake of large particulate matter into a phagocytic vesicle
    - Pinocytosis: non-specific uptake of small molecules and extracellular fluid
    - Receptor-mediated endocytosis: this is specific - the site of endocytosis is a pit coated with clathrin and has receptors that bind to specific substrates
        - Clathrin is a fibrous protein inside the cell that "anchors" the receptor proteins

        - Then the pit invaginates as usual and stuff gets broken down (although the receptor is returned to the coated pit once more)

Cell-Surface Receptors

- The 3 main kinds of cell-surface receptors are ligand-gated ion channels, catalytic receptors, and G-protein coupled receptors
    - Catalytic receptors cause enzyme activity to start or stop when something binds to it (often this enzyme is a kinase or phosphatase)
        - It is often the side chain hydroxyl of serine, threonine, or tyrosine that gets phosphorylated
    - G-protein coupled receptors
        - These work by activating a second messenger, which is a molecule that will spread out to even more receptors to start enzyme activity going
        - So the idea is that the receptor would activate G-proteins which would activate adenylyl cyclase enzymes (for example) which would create cyclic AMP molecules which would activate protein kinases/phosphatases, and thus the effect of a single receptor is multiplied manifold

- Also note that there are inhibitory G-protein linked receptors
- And also that sometimes phosphoplipase C is activated instead of adenylyl cyclase

The Cytoskeleton

- The cytoskeleton not only provides support for the cell, but ALSO helps with movement and substance transport
- Cytoskeleton is made up of microtubules (largest), intermediate filaments, and microfilaments (smallest)…they are all proteins

- The microtubule is made up of alpha and beta globular proteins which are paired up (dimerized) and then made into a sheet which then rolls into a tube
    - We can elongate the tube at the end by adding more alpha/beta sheets, but only at one end because the other end is anchored to the microtubule organizing center (MTOC), near the nucleus
    - Within the MTOC is a pair of centrioles - these are the things which are going to move out to the opposite ends of the cell during cell division

- During mitosis, we have a "mitotic spindle" where we have one pair of centrioles at either end of the cell
    - Some microtubules branch out in a star shape from the centrioles, and we call these the "aster"
    - Other microtubules connect to the chromosomes, and we call these "polar fibers"
        - The polar fibers connect to the kinetochore fibers, which connect to the kinetochore, which connects to the centrosome of the chromosome

- The MTOC is essential for mitosis, but the centrioles are not…(this has been proved experimentally and also by looking at plants, who do not have centrioles)

- Cilia are small hairs on the cell surface which move fluids past the cell surface (think mucociliary escalator)
- Flagellum is a large tail which moves the cell by wiggling
- Both cilia and flagella are made up of a 9+2 arrangement of microtubules, where each microtubule is bound to its neighbor by a contractile protein called dynein which causes movement of the filaments past each other

- And then the cilia/flagella is anchored to the plasma membrane by a "basal body", which has the same structure as a centriole (a ring of 9 triplets of microtubules)
- Note that the structure and motive mechanism is different for prokaryotic cilia/flagella…

- Microfilaments are rods formed in the cytoplasm from the polymerization of the globular protein actin
  - These guys are responsible for gross movements of the entire cell, like pinching it in half during mitosis and "amoeboid movement", when changing the cytoplasmic structure cause the cytoplasm and the rest of the cell to move in one direction

- Intermediate filaments are not composed of a single polypeptide (such as actin, or alpha/beta tubulin)
  - They are also different from microtubules/microfilaments in that they are permanent, not continually re-assembled and disassembled
  - They are good at providing strong cell structure

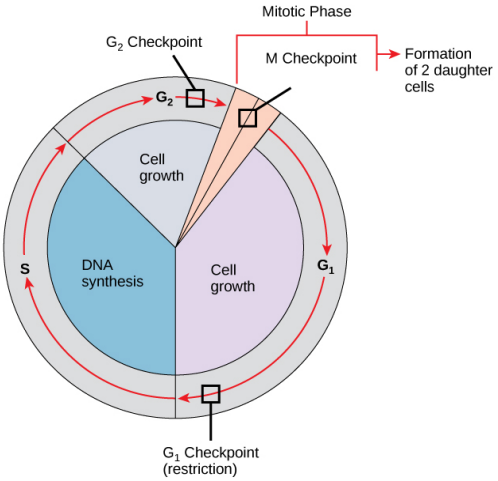
Cell Adhesion and Cell Junctions

- So basically there are different ways to link cells together, and a big determinant of this is whether or not we want to allow substances to go between the cells

- Tight junctions are bands that wrap all the way around the cells
  - This not only prevents the passage of substances between cells, but it also stops proteins in the plasma membrane from going wherever they want - think about intestinal cells, and how the basolateral surface is theoretically continuous with the apical surface, except that since they have these things wrapped all the way around, stuff can't move from the apical to the basolateral
- Desmosomes don't seal cells together but they do attach them by linking in certain spots, not all the way around the cell
  - Basically we have fibers that go all the way between cells, and are anchored in the plasma membranes by a plaque made by the protein keratin and then are further attached to intermediate filaments (thus they don't move within the "fluid mosaic" because they are anchored)
- Gap junctions are opening between cells that allow ions, amino acids, and carbohydrates to mix…but not polypeptides or organelles because they are bigger
  - They also allow for action potentials to pass

<u>Part 3: The Cell Cycle and Mitosis</u>

- See figure: (be sure to label what happens at each phase)



- Some cells are permanently stuck in interphase (think neurons) and thus the only way to replenish them is to develop stem cells from elsewhere
- Cancer occurs when this cell cycle screws up and reproduction happens too fast
    - Sometimes this happens due to a gene which mutates (this is called an oncogene)

Chapter 4

Chapter 4: Genetics and Evolution

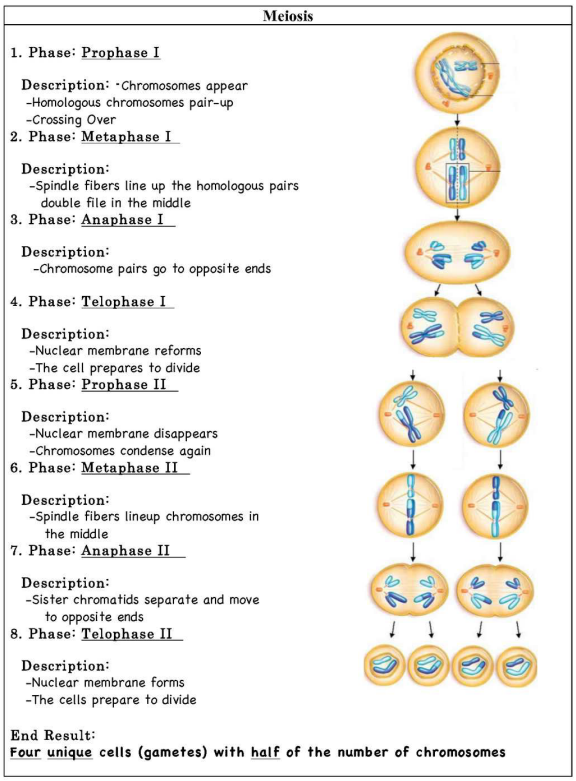
<u>Part 1: Genetics</u>

The Language of Genetics

- Sometimes when the 2 alleles of a gene are different, the dominant allele is not expressed but rather there can be:
    - Incomplete dominance - when there is a blended mix of both alleles (i.e. red + white = pink)
    - Codominance - when the alleles are both expressed, but they are not blended (i.e. think blood cells)
- More complicated stuff can happen during inheritance:
    - Pleiotropism: when altering one gene can seem to affect multiple unrelated things (i.e. eyes, foot)
    - Polygenism: when multiple genes affect a single trait (i.e. more than one gene will affect height)
    - Penetrance: the likelihood that a person with a given genotype will express a certain phenotype (because genes don't always directly lead to certain traits - perhaps they just increase the probability of a trait, like cancer)
    - Epistasis: when the expression of one gene depends on another gene (i.e. allele for curly hair doesn't matter if one is bald)

Meiosis

- See diagram:



- Random notes:
    - The major sources of variability are random segregation and recombination
    - Recombination takes a long time, so meiotic prophase takes most of the time in meiosis
    - Sometimes meiosis II does NOT begin immediately after telophase I

- Non-disjunction is when chromosomes fail to separate during anaphase (either homologous chromosomes in anaphase I or sister chromatids in anaphase II)
- When the non-disjunctive gametes fuse with normal gametes, this can result in:
    - Trisomy (zygote has 3 copies of a chromosome)
    - Monosomy (one copy of a chromosome)
- The effect of trisomy/monosomy (when not fatal) could be:
    - Down's Syndrome (trisomy of #21)
    - Turner's Syndrome (1 X but no Y chromosome)
        - Usually when sex chromosome are involved, external appearance will be male if there is at least one Y chromosome
        - However almost everyone will be sterile and mentally retarded

Mendelian Genetics

- Mendel's Laws:
    - Principle of Segregation: 2 alleles of an individual are separated and passed on to the next generation singly

    - Law of Independent Assortment: the alleles of one gene will separate into gametes independently of alleles for another gene
- Some more terms:
    - Test cross: when we cross a plant for unknown genotype with a (pure-breeding) one of known genotype
    - F1 generation: the progeny of a test cross

Linkage

- Linkage is the failure of genes to display independent assortment (i.e. when they are on the same chromosome)

- In any given cross between genes on the same chromosome, some phenotypes of the progeny will demonstrate linkage and some will not
    - By analyzing the ratio between these two, we can predict how far apart on the chromosome the genes are because we know that crossing over is proportional to distance apart
    - The "frequency of recombination" is given as the number of recombinant phenotypes resulting from a cross divided by the total number of progeny

Sex Linkage and Pedigrees

- Traits determined by genes on the X or Y chromosome are called "sex-linked traits"
    - X-linked traits are frequent, but Y-linked traits are much more rare
    - Men are "hemizygous" for X-linked traits because they only have one X chromosome and thus they express whatever allele they have, even if it is recessive

- Pedigrees are charts of a family that can be used to determine the nature of a gene
- Conventions:
    - Males are squares and females are circles
    - A cross (mating) is represented by a horizontal line connecting the male and female
    - Offspring from a cross are connected to their parents by a vertical line and to their siblings by a horizontal line
    - Individuals afflicted by a trait being studied are shaded in
- Order of analysis:
    - Is the allele that causes the trait dominant or recessive?
    - Is the gene involved carried on a sex chromosome?
    - If the disease is sex-linked, is it on the X or Y chromosome?
    - Calculate the probabilities of inheritance where necessary.
    - If more than one trait is involved, go through Steps 1-4 for each, then determine the relationship between the two traits

Population Genetics

- Population genetics describes the inheritance of traits in populations over time
    - Population is defined as "members of a species that mate and reproduce with each other"
    - Instead of thinking about genomes of particular species, we think about gene pools
    - And a key variable is "frequency of an allele" in a population, which is the number of alleles that exist divided by the number of total alleles

- The "Hardy-Weinberg Law" states that the frequencies of alleles in the gene pool of a popluation will not change over time, provided that the following assumptions are true:
    - There is no mutation
    - There is no natural selection
    - There is random mating

    - There is no migration
    - The population is sufficiently large to prevent random drift in allele frequencies
        - Random drift is when random things happen to change alleles - something which can have a significant effect in smaller populations since by definition they are unable to have enough variability and size to "expunge" the randomness

- We can also use the concept of allele frequency to do this:
    - We know P + p = 1
    - Thus P2 + 2Pp + p2 = 1
        - Then P2 would be the percentage of "PP", 2Pp would be the percentage of Pp, and p2 would be the percentage of pp
        - Also, since we know that allele frequencies tend to remain the same over time, we can conclude that genotype frequencies will also remain constant over time
- We have the idea of "Hardy-Weinberg" equilibrium, which is when the allele frequencies no longer change within a population
    - It takes one generation to reach this - that is, if we start out with mating pure-breeding species, the genotypes of their children will be different from their genotypes, but that's OK because the pure-breeding species were not in H-W equilibrium
    - The true equilibrium takes one generation to achieve

<u>Part 2: Evolution</u>

Evolution by Natural Selection

- A key term in evolution is fitness: it is how successful an animal is in passing on its alleles to future generations (NOT how well they are adapted to an environment, or how well it can feed, etc.)
    - Thus fitness can be conferred simply by having tons of progeny

- Firstly let's note that natural selection will NOT introduce genetic diversity; i.e. it cannot create new alleles…all natural selection does is alter allele frequencies by acting on the genetic diversity present at the time
- However there are some things which DO introduce genetic variability:
    - New alleles: as a result of mutations in the genome (but remember that to have a lasting effect, this mutation must introduce itself in the GERM LINE!)
    - New combinations of alleles: this is when we have independent assortment, recombination, and random segregation during meiosis
        - This will NOT create new alleles, but it can produce different phenotypes that are then "naturally selected on" and thus a certain kind of phenotype will increase in frequency and thus those alleles will as well

- There are different "modes" of natural selection that can have different effects on a population:
    - Directional selection: polygenic traits often follow a bell-curved expression, which means that if we remove the extremes at one end, the entire curve will shift so as to remain "normal"
    - Divergent selection: possibly natural selection could remove the population in the MIDDLE of a bell curve, meaning that we only leave the two extremes - this would split the population in two and possibly even mean the creation of new species
    - Stabilizing selection: select against BOTH extremes of a population, which drives up the number of animals at the average even more
    - Artificial selection: humans intervene by controlling who mates with who
    - Sexual selection: there is no random selection of mating but rather animals would mate with other animals based on mutual attraction due to some mating display

- Kin selection: how sometimes you might sacrifice yourself for your kin and thus the process of natural selection might not work...

The Species Concept and Speciation

- A species is a group of organisms which are capable of reproducing with each other sexually
  - Not only that, but their offspring also have to be capable of reproducing with each other! (thus horses and donkeys are not from the same species because although they can reproduce and create a mule, the mule is sterile)
- There are 2 main classes of reasons why species do not more often try to mate with each other:
  - Pre-zygotic barriers: this is where the hybrid zygote cannot even be formed…for multiple reasons:
    - Ecological (i.e. physical boundaries)
    - Temporal (mating times are not overlapping)
    - Mechanical (i.e. practical size issues)
    - Behavioral (you have to perform a certain ritual first)
    - Gametic (the sperm-egg recognition system doesn't fit)
  - Post-zygotic barriers (prevent the development, survival, or reproduction of hybrid individuals)

- "Speciation" is the creation of a new species…however all new species must come from existing species
- There are different ways this happens, however:
  - Anagenesis is when one biological species simply morphs into another altogether
  - Cladogenesis is when we have "branching", where one species diversifies and becomes 2 or more new species
    - Sometimes this is due to geographical isolation: "allopatric isolation"
    - Sometimes it happens in the same area (perhaps due to divergent selection): "sympatriac isolation"

- We can classify organisms based on these assumptions because we can anticipate species will evolve…for example:
  - We know that related species will share physical characteristics, thus "homologous structures" are physical features shared by 2 different species as a result of a common ancestor
    - Related, "analogous structures" serve the same function in 2 different species but are NOT due to common ancestry
    - A resulting phenomenon is "convergent evolution", when 2 different species come to share A LOT of analogous structures due to similar selective pressures, but it is NOT because they evolved from the same species
      - The opposite of this is "divergent evolution", when divergent selection causes cladogenesis
      - And finally, "parallel evolution" is when 2 species go through similar evolutionary changes due to similar selective pressures

Taxonomy

- We classify organisms in 7 different categories: kingdom, phylum, class, order, family, genus, and species
- Know Table 4.2

- Some important terms:
  - Cephalization means that there is the development of a head region with a brain and sensory organs

- Bilateral symmetry: this is when we split something down the middle and see if the two sides are mirror images of each other

The Origin of Life

- […]

Chapter 5

Chapter 5: Nervous and Endocrine Systems

<u>Part 1: Neuronal Structure and Function</u>

Introduction

- High level: realize that the nervous and endocrine system are interconnected…for example, the pituitary and the adrenals (both endocrine glands) are controlled by the nervous system

Structure of the Neuron

- Cell body (aka soma)
- Dendrites
- Axon
- Axon terminals

- Signal direction goes from dendrites to axon
- Cell body includes the nucleus, as well as most normal cell biology processes…
  - So it has a cell membrane and a cytoplasm as usual…
- Bipolar neurons have one dendrites, while multi-polar neurons have multiple dendrites
  - However, note that all neurons only have ONE axon

The Action Potential

- Go look at an action potential figure (thinking about the cell membrane…)
  - Na, Ca, Cl concentrated outside
    - K concentrated inside
  - Na/K ATP-ase ejects 3 Na and brings in 2 K, but K are allowed to leak back out through K leak channel
    - This results in a negative charge inside the cell of -70 mV (normally)
  - There are 2 main voltage-gated channels - one for Na and the other for K
    - When the membrane potential reaches the threshold (-50 mV), the voltage-gated channels open and we get depolarization
    - Depolarization brings us to +30 mV

- So after each time a neuron fires, there is are 2 refractory periods…
  - ABSOLUTE: the voltage-gated Na channels are resetting and there is no chance for more Na to get through
  - RELATIVE: the membrane is hyper-polarized and so only an extra-large stimulus will set off another action potential
    - This is because the K channels have not closed yet and so lots of negative charge is still coming in (in the form of positive charge leaving…)
- let's talk through it…
  - We're normally at -70 mV but upon the arrival of an extra-cellular signal, we get a bit of sodium coming into the cell…
  - When enough comes in that we get to -50 mV, the voltage-gated Na channels open and positive charge enters the cell until we get to +30 mV

    - At this point, the Na channels close and K channels open so that there is a rush of negative charge into the cell
    - So much negative charge comes into the cell that we actually go MORE NEGATIVE than normal - down to around -90 mV
    - We recover from this state through action via the K leak channels (NOT the voltage-gated ones) and the Na/K ATP-ase

- Let's talk about saltatory conduction…
    - Note that myelin coats the neuron ("myelin sheaths") and there are only openings at specific points along the neuron
        - Myelin is made by Schwann cells
        - Myelin makes the cell membrane impermeable to ions
    - The openings are called Nodes of Ranvier and there are Na voltage-gated channels clustered at the nodes which allow for tons of Na entry at those separated points
    - So this results in rapid conduction and bursts of Na at the nodes - the rapid "jumping" effect which results is known as "saltatory conduction"

Synaptic Transmission

- There are 3 different things which a neuron can synapse onto:
    - Muscle cells
    - Glands
    - Other neurons
- There are different kinds of synapses:
    - Electrical (i.e. gap junctions found in the functional syncytium of the heart)
    - Chemical (where action potential are converted to chemical signals, i.e. neurotransmitters)

    •The ligand-gated Na channels (these open and cause an action potential on the second neuron)
    - The neurotransmitter-containing vesicles in the first neuron
    - The calcium influx
        - This happens on the first neuron as a result of the action potential
        - The calcium causes the vesicles to fuse with the cell membrane and release their neurotransmitters
- After the neurotransmitters are released, they are taken up by the pre-synaptic neuron…then they are either recycled, broken down, etc.
    - i.e. acetylcholinesterase breaks down acetylcholine and thus causes the signal to shut down

- Note that neurotransmitters can be either excitatory or inhibitory - they can either depolarize or hyperpolarize the post-synaptic neuron
    - i.e. GABA causes the membrane potential become more negative
    - Examples of other NT's: gamma-aminobutyric acid (GABA), serotonin, and norepinephrine
- Note that a given pre-synaptic neuron can only release one kind of NT, but a post-synaptic neuron can receive multiple types of NT's (in fact this is probably how spatial summation would work)

Summation

- The first thing to note is that once an action potential begins, the speed and magnitude do NOT change (i.e. the all-or-none principle)
    - The only thing that can affect the speed is the size of the axon
- So the key thing is the regulation of whether or not the action potential fires at all

- The release of neurotransmitters by one AP on one pre-synaptic neuron is usually not enough to bring the post-synaptic membrane to threshold

- So the decision is made…based on how many EPSP (excitatory post-synaptic potential) and IPSP (inhibitory post-synaptic potential) we get…
- There are also 2 kinds of summation:
    - Temporal (when a single axon terminal fires so quickly that the effects of multiple fires combine)
    - Spatial (we combine the effects of multiple axon terminals to see if they lead to a depolarization exceeding -50 mV)

<u>Part 2: Organization of the Human Nervous System</u>

Functional Organization

- There are 3 functions of the nervous system:
    - Sensory - receive information coming from the outside to the inside
    - Integrative - processing the information and deciding what to do with it
    - Motor - sending information from the CNS to the effectors (thus it is not only muscle they innervate, but glands as well)

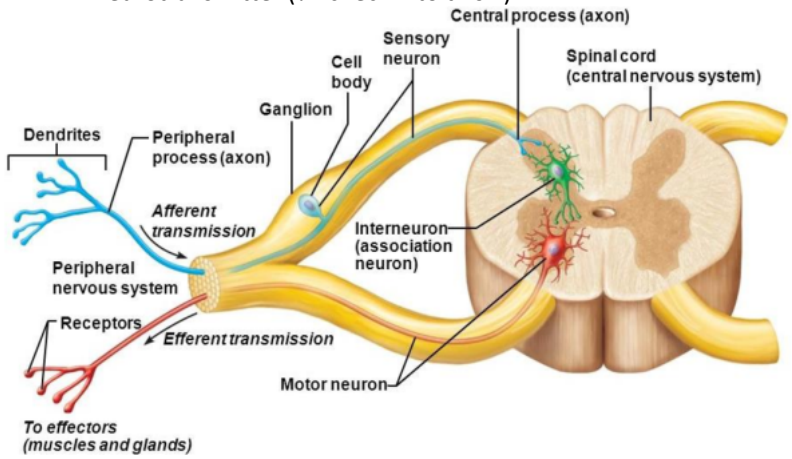
- So there are different kinds of neurons to go along with this:
    - Afferent: carry information from the sensory organs to the CNS
    - Efferent: carry information from the CNS to the effectors
        - i.e. motor neurons

- Reflex arcs: these things are nervous system pathways that start with something being sensed and end with an effector performing some action
    - Mono-synaptic reflex arc: this is when there are just 2 neurons and 1 synapse involved, for example if a sensory neuron senses a muscle stretching, then sends the single along its axon to the spinal cord where it synapses with a motor neuron, which sends back a signal to some muscle to contract in response
    - Di-synaptic reflex arc: when the sensory neuron synapses with more than one post-synaptic neuron
        - So not only the motor neuron…
        - But also synapse with an "inhibitory interneuron" which would then go and synapse with a neuron controlling another muscle to cause it to relax
        - So we end up with one muscle contracting and the other relaxing (this is an example of reciprocal innervation)

- Let's talk about the organization of the nervous system
    - Somatic vs. autonomic:
        - Somatic is skeletal muscle (mostly voluntary reflexes) and conscious sensation
        - Autonomic is smooth muscle and internal organs (mostly involuntary)
            - Note that both somatic and autonomic have afferent and efferent functions
    - We can further break down the EFFERENT part of the autonomic division into sympathetic and para-sympathetic:
        - Sympathetic is associated with the fight or flight response, adrenaline, epinephrine, etc. (basically dealing with stress)
        - Parasympathetic is associated with resting and "ruminating" (means the digestion of food)

Anatomical Organization

- See Figure:
    - Ganglions are a cluster of soma (cell bodies) which are located outside the CNS (OUTSIDE!)
    - Sympathetic ganglion are interconnected so that the fight/flight response can be coordinated
    - Between epinephrine and norepinephrine: one is a hormone and the other is a neurotransmitter (? - check into this…)



- CNS anatomical organization

- PNS anatomical organization
    - All neurons entering and exiting the CNS are carried by 12 pairs of "cranial nerves" (go to the brainstem) and 31 pairs of "spinal nerves" (go to the spinal cord)
    - Other than that, we have to understand that there are different nerve organizations for the somatic nervous system, the autonomic sympathetic nervous system, and the autonomic parasympathetic nervous system

- Somatic nervous system
    - Afferent
        - So now we are talking about sensory neurons…
        - The neuron set-up is that we have a long dendrite going from the sensory receptor (let's say the skin on the back of the hand) to the cell body, which is located in a "dorsal root ganglion"
            - The dorsal root ganglion is a bunch of somatic sensory cell bodies clumped together, and it is "dorsal" meaning that it is "to the back of" the spinal cord
            - It is protected by the vertebral column but not by the meninges
        - Then from that cell body, the axon extends into the spinal cord where it synapses somewhere either in the spinal cord or the brain stem
    - Efferent
        - First realize that it is the somatic NS, meaning that only skeletal muscle cells are innervated, meaning that the only efferent neurons are MOTOR NEURONS
        - The motor neurons have cell bodies (and therefore dendrites) in the brain stem or ventral (front) portion of the spinal cord, and then have a long axon to the skeletal muscle
            - They use acetylcholine as their neurotransmitter
- Autonomic nervous system
    - Afferent
    - Efferent

- One characteristic common to both sympathetic and parasympathetic is that instead of a single neuron going from CNS to effector, there are two: called the "pre-ganglionic" and "post-ganglionic" neurons
- This is because we have one neuron coming out of the spinal cord, but instead of going to the effector it goes to a ganglion (cluster of cell bodies)…and then from there another neuron comes out to go to our effector
- The sympathetic and para-sympathetic differ in terms of the location of the ganglion, the types of neurotransmitters used, etc…See table:

Autonomic Innervation of Selected Body Structures

Structure	Sympathetic	Parasympathetic
eye - pupil (iris)	dilation	constriction
heart	increased rate & force	decreased rate
lung bronchioles	dilation	constriction
gut wall	decreased motility	increased motility
gut sphincter	constrict	relax
bladder detrusor	relax	contraction
bladder-urethra smooth sphincter	constrict	relax
penis (etc.)	ejaculation	erection
gallbladder bile & duct	relax	contract
salivary glands	concentrated viscous saliva	abundant watery saliva
nasal & lacrimal glands	vasoconstriction	abundant secretion

- The adrenal gland is an important part of the nervous system - there are 2 of them, one above each kidney
- There are 2 parts to the adrenal gland: cortex (outer portion) and medulla (inner portion)
    - The cortex is an endocrine gland - it secretes glucocorticoid (aka cortisol) and mineralocorticoid (aka aldosterone)
    - The medulla is part of the sympathetic nervous system - it is basically an evolved bunch of post-ganglionic neurons that are stimulated by pre-ganglionic neurons
        - When they are stimulated, they release epinephrine (aka adrenaline), which is a fast-acting hormone that plays a big role in the fight-or-flight response
- So remember: norepinephrine is an NT, while epinephrine is a hormone (aka ADRENALINE)

<u>Part 3: Sensation</u>
Types of Sensory Receptors
Gustation and Olfaction
Hearing and the Vestibular System
Vision: Structure and Function

<u>Part 4: The Endocrine System</u>
Hormone Types: Transport and Mechanisms of Action

- Let's review the difference between endocrine and exocrine glands…
    - Endocrine glands are DUCTLESS glands that secrete products into the bloodstream via capillaries such that the products eventually go to other cells with appropriate receptors
    - Exocrine glands are those whose products empty into the external world via DUCTS
        - Note that the GI tract counts as the external world (thus the pancreas is an exocrine gland)

- The two types of steroid hormones are peptide hormones and steroid hormones…there are significant differences between the two, see table:

- Other facts about hormones:
    - Peptide hormones are divided into two types: polypeptides and amino acid derivatives
        - Glucose is an example of a polypeptide
        - Epinephrine is an example of an amino acid derivative - it is based on tyrosine and secreted by the adrenal medulla
    - As for steroids, the **only** body parts which secrete them are:
        - For sexuality, reproduction, development etc: the testes, ovaries, and placenta
        - For water balance and other processes: adrenal cortex

Organization and Regulation of the Human Endocrine System

- Endocrine system is all about maintaining homeostasis: which is to keep the body conditions within certain limits
    - i.e. Calcitonin - decreases calcium concentrations in the blood

- You have to realize that there are multiple levels of hormonal control
    - The lowest level is how hormones directly control bodily functions, for example aldosterone would affect water retention in the kidneys
    - But then there are "tropic hormones", mostly released by the anterior pituitary, which control those hormones by inhibiting or stimulating their release
    - And then even on top of the tropic hormones, there is a neurological layer of control in that the hypothalamus (brain tissue!) releases "releasing" and "inhibiting" factors (aka hormones) to the pituitary so as to control the tropic hormones

- The hypothalamic-pituitary control axis…
    - This control axis is basically the relationship between the hypothalamus and the pituitary gland

    - The two are connected via the "hypothalamic-pituitary portal system" aka the "hypothalamic-hypophysial portal system" (since the pituitary gland is also known as the hypophysis)
- The hypothalamus is divided into…
    - Anterior (adenohypophysis): this is a normal endocrine gland in that it is affected by the releasing/inhibiting factors and it releases hormones
    - Posterior (neurohypophysis): this is a neuroendocrine gland in that it is composed of brain tissue (hence "neuro") but it releases hormones
        - Actually the hormones are made in the hypothalamus and released from the posterior pituitary…the posterior pituitary is basically just a bunch of axons

Major Glands and their Hormones

- **Memorize Hormones**

[Chapter 5 Addendum]

CNS Anatomical Organization

- **[fill this in…!]**

Part 3: Sensation

Types of Sensory Receptors

- Two very broad categories of sensory receptors are exteroreceptors (detect stimuli from the outside world) and interoreceptors (detect internal stimuli)

- There are 5 types of sensory receptors: mechanoreceptors, chemoreceptors, nociceptors, thermoreceptors, and electromagnetic receptors
    - Mechanoreceptors: most basically, these receptors respond to mechanical disturbances such as pressure, vibration, etc.
        - For example we have the Pacinian corpuscle, which sends an action potential whenever its membrane is depressed
        - Also there is the auditory hair cell, which (as we will later discuss) is in the inner ear and detects vibrations from sound waves
        - Also, those things that detect stretch in the intestinal wall and signal that gastrin release are mechanoreceptors
    - Chemoreceptors: these guys (predictably) respond to particular chemicals
        - For example, olfactory receptors detect airborne chemicals
        - Gustatory chemoreceptors detect chemicals in the food we eat which give it its taste
        - Chemoreceptors in the medulla as well as carotid and aortic arteries detect changes in blood pH, CO_2, O_2, etc.
    - Nociceptors: these are pain receptors which work by detecting chemicals that are released when tissue is damaged (yes, this means that they are simple chemoreceptors in a way)
        - One thing that we notice with these guys is that they can be imprecise -- that's why we get things like referred pain, which is when we feel pain in our arm during a heart attack for example
    - Thermoreceptors: changes in temperature
    - Electromagnetic receptors: stimulated by electromagnetic waves -- i.e. the rods/cones of the eye!

- There are also proprioceptors:

- These are basically receptors which allow us to be aware of ourselves -- i.e. what position is our body in, etc.

Gustation and Olfaction

- OK first, this is just an application of chemoreceptors

- Gustation is taste, and basically there are 4 main kinds of taste receptors on the tongue that respond to different chemicals and tell us what we are "tasting"
  - Sweet receptors detect glucose
  - Salty receptors detect sodium (Na+)
  - Bitter receptors detect basicity
  - Sour receptors detect acidity
- The unit of taste is the "taste bud", and it consists of epithelial cells surrounding a "taste pore" where the hairs are located which detect those different things

- Olfaction is taste, and here the receptors are high in the nasal cavity
- Chemicals in the air come through the mucus

Hearing and the Vestibular System

- Introduction
  - Discuss the anatomy of the ear.
    - It is divided into the outer, middle, and inner ear:
      - Outer:
        - The PINNA directs sound waves into the ear
        - The sound waves travel through the EAR CANAL which is sealed at the end by the TYMPANIC MEMBRANE (aka eardrum)
      - Middle:
        - Overall it is just an AIR-FILLED CAVITY that links up with the NASOPHARYNX through the EUSTACHIAN TUBE
          - Usually the Eustachian tube is blocked but sometimes it is open so that the pressure from inside the ear can equilibrate with atmospheric pressure during things like yawning
        - Inside this air-filled cavity we have THREE SMALL BONES: the malleus (hammer), incus (anvil), and stapes (stirrup)
          - These bones are all attached by "HINGES" - and the malleus is connected to the tympanic membrane and the stapes is attached to the membrane which separates the middle ear from the inner ear (this is how sound from the outside gets conducted through this inner portion!)
      - Inner:
        - OK here there are TWO major sensory structures, each with a different purpose:
          - VESTIBULAR APPARATUS: it is for our sense of equilibrium (more on this later)
          - COCHLEA: it is like a coiled tube like a snail that lies within a bony cavity called the LABYRINTH
            - It is separated from the middle ear by the OVAL WINDOW and ROUND WINDOW
- Hearing is our perception of sound
  - What do we remember from physics that is important here?

        - High vs. low sounds (i.e. pitch) correspond to high-frequency and low-frequency waves
        - Soft vs. loud sounds correspond to the AMPLITUDE of the wave
- Sound transduction is a multi-step process
    - What's the overall pathway for how hearing works?
        - Air waves -> mechanical vibrations -> fluid waves -> chemical signals -> action potentials
    - Go into a little more detail for each step.
        - The sound waves travel through the ear canal and hit the tympanic membrane, which causes the three bones in the middle ear to vibrate in sequence
        - The last bone in the sequence (STAPES) is attached to the OVAL WINDOW which is connected to the cochlea of the inner ear
        - The cochlear has fluid in it and waves are created in this fluid which activate the SENSORY HAIR CELLS inside the cochlear as they move through
        - The waves move through the entire cochlea and the vibration energy "exits" at the ROUND WINDOW, which goes back into the middle ear area
        - The hair cells get stimulated and action potentials are fired in the primary sensory neurons which bring the signal to the brain, and off we go!
- The cochlea of the inner ear is filled with fluid
    - Discuss the anatomy of the cochlea in more detail.
        - There are 3 parallel "channels" which are filled with fluid: vestibular duct, cochlear duct (in the middle), and tympanic duct
            - The vestibular and tympanic ducts are continuous (they meet at the tip of the cochlear at the opening known as the HELICOTREMA) and they contain fluid known as PERILYMPH
            - The cochlear duct is filled with ENDOLYMPH
        - The cochlear duct contains the ORGAN OF CORTI, which is where all the action happens:
            - OK so the organ sits on the BASILAR MEMBRANE and is covered by the TECTORIAL MEMBRANE
            - When fluid waves move through the cochlea, they displace these membranes and they cause the hair cells of the organ of Corti to move side to side
                - The idea is that there are STEREOCILIA sticking out of the hair cells and they have "protein bridges" between them. When the cilia bend/move around as waves pass by, these bridges are affected and they respond by opening ion channels to allow calcium release, action potentials, etc.
                - Ultimately the signals get passed down the COCHLEAR NERVE
- Sounds are processed first in the cochlea
    - Explain how we account for different PITCHES of sound.
        - OK this is all about the BASILAR MEMBRANE (remember what that is?). The parts of the membrane that are near the round and oval windows is STIFF AND NARROW, but it is wider and more flexible in the middle of the cochlea (the part furthest from the round/oval windows)
        - And the higher-frequency waves create maximal displacement of the basilar membrane NEAR the windows, whereas the lower-frequency waves displace maximally at that distal end
        - Thus by figuring out where the hair cells are sending the most action potentials, we can figure out the frequency of the waves and thus the pitch! Pretty sick!
    - How about loudness?
        - OK this is a little more basic - it's just the amplitude of the wave, which will affect the FREQUENCY of the action potentials sent

- Hearing loss may result form mechanical or neural damage
    - Discuss the 3 forms of hearing loss.
        - Conductive hearing loss: sound can't get through the external or middle ear. This could be as simple as ear wax plugging the ear canal to diseases which impede the vibration of one of the bones
        - Sensorineural hearing loss: this is when the structures of the inner ear get damaged. For example, hair cells can degenerate over time and cause presbycusis
        - Central hearing loss: the neural pathway from the ear to the central cortex is damaged (this is the most rare)

- As for the EAR AND EQUILIBRIUM...
    - The semi-circular canals of the ear detect motion and therefore help the body to maintain equilibrium
    - Just like with sound, they work on the basis of hairs detecting movement and then sending neural impulses
    - Other balance-monitoring organs in the ear:
        - Utricle -> for static equilibrium
        - Saccule -> for linear acceleration

Vision: Structure and Function

- Introduction
    - How does vision work? How is this related to the way a camera works?
        - Because light enters the eye through the PUPIL and is focused by a LENS on a light-sensitive surface -- the RETINA
            - Just as with a camera, the pupil can adjust to control how much light gets in
        - Then the photoreceptors of the retina transduce light energy into an electrical signal
        - Then the signal goes through various neural pathways
- The Eye is Protected by the Skull
    - Discuss the EXTERNAL anatomy of the eye.
        - It's pretty basic…we have a bony cavity in the face called an ORBIT that is formed by the facial bones of the skull
        - There are 6 EXTRINSIC EYE MUSCLES which attach to the outer surface of the eye and control its movement
        - The eyelids close over the top part of the eye
        - The LACRIMAL APPARATUS is a system of glands and ducts that keeps a flow of tears washing over the cornea so that it is moist and clean
            - The NASOLACRIMAL DUCT drains these tears into the nasal cavity
    - Discuss the INTERNAL ANATOMY of the eye.
        - There are 2 compartments of the eye, and they are separated by a LENS
            - FRONT COMPARTMENT:
                - This is mostly filled with AQUEOUS HUMOR, a low-protein plasma-like fluid
            - BACK COMPARTMENT: this is mostly filled with the VITREOUS BODY, which is a matrix that helps maintain the shape of the eyeball
    - Talk about the path of light through the eye.
        - It comes through the CORNEA, which is a transparent disk continuous with the SCLERA
        - Light goes through the aqueous humor, through the opening of the pupil, and hits the LENS
        - The light rays are bent so that they focus on the RETINA

            - There is a spot on the retina called the OPTIC DISK, from which neurons of the visual pathway exit the eye as the OPTIC NERVE
            - Right next to this optic disk is the FOVEA surrounded by the MACULA, which together are the regions of the retina with the MOST ACUTE vision
- Photoreceptors Transduce Light into Electrical Signals
    - Quickly compare/contrast rods and cones.
        - Rods and cones are the 2 kinds of PHOTORECEPTORS in the eye
        - Rods are OVERALL more numerous (20:1 ratio), but cones are more concentrated in the FOVEA
        - Rods are more for mono-chromatic night-time vision and low-light environments, while cones are good for HIGH-ACUITY and COLOR vision during the daytime
    - Discuss the structure of rods and cones.
        - OK there are THREE main segments:
            - Outer segment that touches that PIGMENT EPITHELIUM of the retina
            - Inner segment that holds the major organelles like nucleus, ATP/protein synthesis, etc.
            - Base segment that synapses with the bipolar cells
    - Talk about visual pigments. How do they work?
        - These are bound to the cell membranes in the OUTER SEGMENTS of the photoreceptors
        - Their job is to do the ACTUAL TRANSDUCTION from light energy to a change in membrane potential
        - Rods have ONLY ONE kind of visual pigment: RHODOPSIN
            - Cones have 3 different kinds but they are all closely related to rhodopsin
            - Each of the 3 cone pigments absorbs a particular wavelength of light the most - RED, GREEN, or BLUE (these are the basic colors of light, as you know)
    - So what actually happens when the light hits those rods or cones?
- Defects in visual acuity
    - Alright, so the deal is that light goes through the cornea and the lens before hitting the pupil
        - Both the cornea and the lens change the path of the light to a certain degree such that the rays arrive exactly on the retina
        - However, if the cornea/lens are improperly bent, the light may be focused too far in front of the retina, or too far behind it
    - There are 3 ways this can go wrong:
        - MYOPIA: light is focused in front of the retina -- this causes nearsightedness
            - We correct this by putting a concave (diverging) lens in front of the eye
        - HYPEROPIA: light is focused behind the retina -- this causes farsightedness
            - We correct by putting a convex (converging) lens in front of the eye
        - PRESBYOPIA: in general, the inability to accommodate (focus) -- this occurs when the lens loses flexibility due to aging

Chapter 6

Chapter 6: Circulatory, Lymphatic, and Immune Systems

Part 1: The Circulatory System

Components of the Circulatory System

- The circulatory system handles many duties:
    - Distribution of nutrients from the digestive tract, liver, and adipose (fat) tissue
    - Transport oxygen from the lungs to the entire body, and carbon dioxide from the tissues back to the lungs
    - Transport metabolic waste products from tissues to the excretory system (i.e. the kidneys)
    - Transport hormones from the endocrine glands to the targets and provide feedback
    - Maintain homeostasis of body temperature
    - Hemostasis (blood clotting)
- Some terms:
    - Perfusion: the flow of blood through a tissue
    - Ischemia: inadequate blood flow through a tissue (results in predictably…build-up of waste, inadequate oxygen distribution, etc.)
    - Anoxia: blood flow is OK, but oxygen distribution is reduced

- Of all the different things that blood travels through (heart, veins, arteries, etc.) - the capillaries are the structures which allow materials from the blood to diffuse into the surrounding tissue (this because their walls are thin enough)

- The heart can be divided (on a macro level) into two sides - left and right
    - The right side of the heart pumps blood to the lungs (this is called the pulmonary circulation), and the left side pumps the oxygenated blood to the rest of the body (this is called the systemic circulation)
- Now think capillaries again - capillaries are the only place where blood's contents can be exchanged with the surroundings, and so in each circulation system they will only pass through one set (either in the lungs or in the tissues) before going back to the heart
    - However, there are things called "portal systems" where blood passes through 2 sets of capillary systems before returning to the heart
    - There are 3 portal systems:
        - Hepatic (blood goes through intestinal capillaries, then into the hepatic vein, then through liver capillaries, then finally back to the heart)
        - Hypothalamic-hypophyseal portal system (blood passes through capillaries in the hypothalamus and then also in the pituitary gland)
        - Kidney
    - The idea is that portal systems are for direct transport of substances from one place to another, without having to go through the heart

The Heart

- Each side of the heart (right/pulmonary and left/systemic) has two chambers: atrium and ventricle
    - The blood arriving from veins collects in the atrium and then is pumped into the ventricle and then into the arteries to either go to the brain or the rest of the body

- The heart has its own nutrient needs, so there is are "coronary arteries" which branch from the aorta and then surround the wall of the heart (like a crown, hence "coronary"), eventually end up in the coronary veins which empty into the coronary sinus which empties into the right atrium

- Valves in the circulatory system are used to ensure that blood only flows one way - bi-directional flow can be a problem due to pressure differentials (for example, the right ventricle is of higher pressure than the right atrium, so unless there was a valve between the two, we would see blood going from the ventricle into the atrium which is not productive

    - Right atrioventricular valve: bicuspid aka mitral valve
    - Left atrioventricular valve: tricuspid valve
    - Semilunar valves: between the large arteries and the ventricles
    - Valves in the venous system - this is necessary because after the blood passes through the capillaries, a lot of its "pressure" is gone and so it is harder for it to continue moving forward
        - Contraction of skeletal muscle also helps this because it squeezes the veins and thus increases the pressure within them

- A cardiac cycle is made up of diastole and systole
    - Diastole: when the AV valves are open and the atria are squeezing blood into the ventricles
    - Systole: when the AV valves are closed but the semilunar valves are open as the contraction of ventricles sends blood into the arteries
        - At the beginning of systole, the AV valves close ("lub")
        - At the end, the semilunar valves close ("dub")

- Cardiac output (L/min) = stroke volume (L/beat) * heart rate (beats/min)
    - Athletes (who have stronger hearts) have lower heart rates because their stroke volumes are higher

- One way to increase stroke volume is to stretch the heart more, since it will contract more forcefully to return to its original state
    - The way to do this is called the "Frank-Starling mechanism", which is when we increase venous return, which means putting more blood into the heart from the veins
    - There are 2 main ways to increase venous return:
        - Increase the total volume of blood in the circulatory system (by retaining water)
        - Contract the large veins

- Action potentials causing contraction of the cardiac muscle are spread through the muscles of the heart because the cells act as a "functional syncytium", which means that for all intents and purposes, the cells are connected because there are gap junctions between the cells that allow electrical signals to move from cell to cell
    - The atria's functional syncytium (and therefore the signals that pass through it) is isolated from the ventricular syncytium by the "cardiac conduction system"
- Recall from another chapter that not only do voltage-gated ("fast") sodium channels propagate the action potential, but "slow calcium channels" do as well because they stay open longer and thus the possibility of tetanus/signal build-up is eliminated
    - There are involutions of the membrane in cardiac cells called t-tubules, which allow the voltage depolarization to reach the heart of a cell - this causes the SR to release calcium and also allows the entry of calcium from the extracellular environment (of course as you recall, calcium is necessary for muscle contraction)

- Unlike skeletal muscle, the action potentials in the heart are not started by nervous or endocrine signals - instead they are started automatically from within the heart - a region of the right atrium called the sinoatrial (SA) node
- In these cells, the voltage difference never returns to -90 mV (as the rest of the body does) but rather just to -55 mV, which means that the spontaneous leakage of sodium into the cell can set off the voltage-gated sodium channels
    - The only thing is, these are "slow" channels, and so the depolarization/repolarization of the SA node cells is quite a bit slower…

- So once an action potential starts in the SA node, it goes into the atria but also through the "internodal tract" to the atrioventricular node, where it pauses for a second (to allow the action potential and associated contraction to spread throughout the atria) and then into the AV bundle (aka bundle of His) then into the Purkinje fibers, which spread out to cover the ventricles
    - Note that the fibers spread out from the bottom of the ventricles upwards, so that the blood is pumped upwards from the ventricles to the aorta/arteries

- The autonomic nervous system (as mentioned) doesn't cause the heart to beat, but it can regulate how FAST it beats by inhibiting the depolarization of the SA node
    - It is the parasympathetic system that does this, and the main nerve is called the "vagus nerve", which has preganglionic axons synapsing in ganglia near the node, then post-ganglionic axons going from the ganglia to the SA node and releasing Ach to inhibit the SA node (this is called the "vagal tone")
    - The sympathetic nervous system also affects the heart - this happens when the heart needs to be beat quicker/output more per beat
        - Sympathetic post-ganglionic neurons innervate the heart by releasing norepinephrine
        - The adrenal medulla secretes epinephrine which binds to receptors on the heart

Hemodynamics

- Blood flow is basically the result of opposing forces: the difference in pressure between arteries and veins vs. the friction from the walls of the vessel (called "resistance")
    - The equation describing this is Ohm's law: (delta)P = Q x R (P = pressure, Q = blood flow, R = resistance)
        - We change pressure by increasing the force or rate of cardiac contraction
        - We change resistance by constricting arteriolar smooth muscle (called precapillary sphincters) so that the arteries are slower, which increases resistance

- Peripheral resistance is the resistance of the entire systemic circuit
    - The peripheral resistance is controlled by the sympathetic nervous system - it is always providing at least a base level of resistance by innervating the precapillary sphincters - this constant nervous system input is called "adrenergic tone"
    - The sympathetic nervous system is also able to divert blood flow to tissues which need it more at certain times…

- For a blood pressure of 120/80:
    - Systolic blood pressure: 120 mmHg
    - Diastolic blood pressure: 80 mmHg
    - Pulse pressure: 40 mmHg

- Blood pressure is taken with a sphygmomanometer, which is a blood pressure cuff
    - The cuff cuts off blood flow to the arm below it and then the pressure is released until an audible sound is heard - this is the "systemic arterial pressure", because it means that the pressure in the artery is just high enough to overcome the pressure of the cuff
        - When we can hear sounds the first time, we say that it is the "systolic pressure" because that is the highest pressure which there will ever be -- it is the arterial blood pressure right after systole
        - Then the cuff continues to be loosened until the sound cannot be heard anymore - this is because the cuff is loose enough that the blood flows smoothly through the upper arm arteries and does not "pound" into the sides

of the walls when it is going through the formerly restricted area where the cuff was - this is the diastolic pressure
    - Note that diastolic pressure remains high even between heartbeats because the walls of the aorta/arteries are elastic and muscular, so they shrink a lot when not filled with blood to maintain the same pressure
        - This is important because that high pressure needs to be maintained in order to drive blood flow throughout the body at all times

- Lastly, there is the concept of "local autoregulation", which is when the tissues control the resistance (i.e. dilation) of the capillaries in their local area according to how much nutrient intake/waste management they need
    - This is good because then the nervous system doesn't have to do all this work controlling everything

Components of Blood

- There are 2 parts to blood - the part that is liquid ("plasma") and the part that is composed of cells (called "formed elements")
    - Plasma consists of 55% of the blood volume, and it contains a bunch of stuff that is just dissolved, such as electrolytes, buffers, sugars, blood proteins, lipoproteins, carbon dioxide, oxygen, metabolic waste products, etc.

- The blood proteins include:
    - Albumin: helps to maintain oncotic pressure, which is the portion of osmotic pressure in the capillaries due only to the plasma proteins
    - Immunoglobulins: essentially they are antibodies, thus they are important for the immune system
    - Fibrinogen: this is essential for blood clotting
    - Lipoproteins: you know what these are…

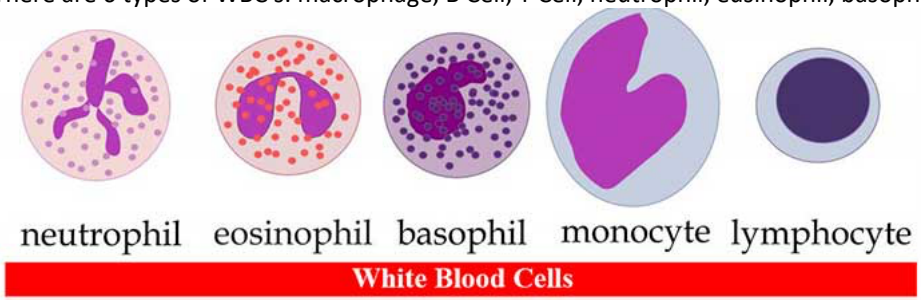
- Other dissolved substances:
    - Sugars: are mostly glucose
    - Waste products: mostly urea (nitrogen breakdown product of amino acids), bilirubin (breakdown product of heme)

- The other component of blood (besides plasma and all the dissolved things inside it) is the formed elements - red blood cells (erythrocytes), white blood cells (leukocytes), platelets, etc.
    - RBC's are 40-45% of all blood (so they are the majority of the formed elements)
        - This portion is known as the "hematocrit"
    - WBC's/platelets are around 1% of the total…
- All blood cells are made from stem cells in the bone marrow

- When whole blood clots, there is a fluid portion and a solid clot - the fluid portion is serum, which is made up of plasma minus the proteins in it used for clotting (think fibrinogen)

- RBC stuff
    - The hormone erythropoeitin (made in the kidney) stimulates RBC production in the bone marrow
    - Aged RBC's are eaten by phagocytes in the spleen and liver
    - RBC's last 120 days
    - It has no nucleus or other organelles - it must rely on glycolysis for ATP (that's why it is an obligatory glucose user)
    - It has a biconcave shape because it needs to maximize its surface area because it carries a lot of oxygen from lungs to tissues and carbon dioxide from tissues to lungs

    - It contains millions of hemoglobin molecules, which is what allows it to carry oxygen
- WBC stuff
    - The leukocyte (WBC)'s role is to fight infection and dispose of cells
    - WBC's are normal cells (i.e. they have all the organelles)
    - Some WBC's (macrophages and neutrophils) move by amoeboid motility (crawling), which means that they can crawl out of capillary intercellular junctions and roam free in TISSUES so as to hunt enemies
    - There are 6 types of WBC's: macrophage, B Cell, T Cell, neutrophil, eusinophil, basophil



- Platelet stuff
    - They are like RBC's in that they have no nuclei and a limited lifespan
    - Their function is to aggregate at the site of damage to a blood vessel wall and form a "platelet plug", which will help to stop bleeding
        - Another blood protein called fibrin forms a mesh to hold the platelet plug together
            - Fibrin comes from the plasma protein fibrinogen - this is catalyzed by another protein called thrombin
            - *So a plasma protein is just a protein dissolved in the plasma!*
        - When everything tries, it becomes a scab
            - A blood clot or "thrombus" is just a scab floating in the bloodstream -- not good!
    - Lots of other substances are involved in hemostasis - including Vitamin K, which a lot of the proteins depend on

Transport of Gases

- Oxygen transport
    - Oxygen is carried on hemoglobin, which is a complex protein in RBC's
        - Hemoglobin has 4 polypeptide subunits, each subunit containing one molecule of heme
        - Heme is a large multi-ring structure that has a single iron atom bound at its center
        - The iron atom binds to oxygen
    - Remember that hemoglobin demonstrate "cooperative" binding, which is when we have a tense/relaxed conformation for the hemoglobin molecules
        - When it is tense, the affinity for oxygen is lower…and vice versa for relaxed
            - The idea is that the more subunits bound, the higher the affinity of the other subunits for oxygen...
        - This is important so that it can have lower affinity in the tissues (so that myoglobin can take it) but higher in the lungs (so that it can take the oxygen from the alveoli)
    - Certain factors stabilize the tense configuation, meaning that in the presence of these factors, hemoglobin is more likely to be tense
        - These factors abound in tissues which are in need of oxygen:

            - High CO2 partial pressure (would be the case with a lot of glycolysis/CAC stuff)
            - Decreased pH (from lactic acid build up)
            - Increased temperature (again as a result of all this metabolic activity)
        - The lessened affinity of hemoglobin in response to these factors is called the "Bohr effect"
- Carbon dioxide transport
    - CO2 is transported through the blood in 3 main ways:
        - As carbonic acid/protons, due to the equilibrium of $CO_2 + H_2O$ <--> H_2CO_3 <--> $HCO_3^- + H^+$
        - Bound to hemoglobin (but not the oxygen binding sites)
        - Dissolved in the blood (it is a bit more polar than O2 and so it can dissolve)

Exchange of Substances Across the Capillary Wall

- 3 kinds of things need to be able to pass between the endothelial cells that make up the capillary wall: nutrients, waste products, and WBC's
- The entry and exit of water from the capillaries is important to note:
    - Firstly, realize that water has a great tendency to flow OUT of the capillaries because of a) the fluid pressure created by the heart's pumping action and b) the high osmolarity of the tissues
    - We deal with this by making the plasma of the blood ALSO of very high osmolarity - this is where albumin comes in, because it is too large to leave the capillaries and so it will stay in the bloodstream and give it high osmolarity
        - As we discussed earlier, the part of osmotic pressure caused JUST by these proteins is the "oncotic pressure"
            - Think about it…something like NaCl in the bloodstream would NOT help the osmotic gradient because it can leave the capillaries and go into the tissues as well!
- As we go through a capillary, we will see that water squeezes out of the tissues at the beginning, but as we get closer to the end, the fluid pressure decreases and the oncotic pressure becomes more powerful, resulting in water coming BACK into the capillary from the tissues

- There are some medical conditions related to water in the tissues:
    - During inflammation, the endothelial cells of the capillaries retract so that the intracellular clefts are bigger so that more white blood cells can get to the tissues
        - But this means that water can get into the tissues as well, causing them to swell and producing a condition known as "edema"

The Lymphatic System

- This is another system for fluid distribution in the body
- It is not "connected" to the heart, so flow through this system is managed by valves, smooth muscles in the walls, etc.
- The fluid flowing through this (called "lymph") is filtered by lymph nodes, which are part of the immune system - they contain tons of WBC's that can initiate an immune response to anything foreign in the lymph…
- The biggest lymph vessel is the thoracic duct, which smaller lymph vessels empty into…the thoracic duct empties into the left subclavian vein (near the neck)

<u>Part 2: The Immune System</u>

- There are 3 kinds of immunity: innate, humoral, and cell-mediated

Innate Immunity

- This is general, non-specific protection which the body provides against various invaders

- Here are the main components of innate immunity:
    - Skin (stops the entry of micro-organisms)
    - Tears, saliva, and blood (contain lysozyme, which kills bacteria)
    - Gastric (stomach) acidity, which destroys many pathogens which are ingested with food or swallowed after being passed out of the respiratory tract
    - Macrophages and neutrophils indiscriminately phagocytize micro-organisms
    - The "complement system", which is a group of 20 blood proteins that non-specifically bind to the surface of foreign cells and destroy them

Humoral Immunity, Antibodies, and B-Cells

- Now we are talking about antibodies (Ab) or also known as immunoglobulins (Ig), which recognize cells specifically, bind to them, then destroy them
    - Each anti-body molecule is composed of 2 copies of 2 different polypeptides - the "light chain" and the "heavy chain"
    - Also, the anti-body molecule can be divided into the "constant region" and the "variable region"
        - The "constant region" is the same for all the antibodies in the same CLASS - the classes being IgG, IgA, IgM, IgD, and IgE
        - The variable regions are variable because they are the parts that recognize different antigens and bind to them
            - The antigens are the things on the bad cells that identify them to the antibodies…they can be a protein on the cell surface, sometimes the entire cell (when it is small)
                - As you would expect, many times the "fitting" is based on 3-D conformation

- When an anti-body binds to an antigen, different things can happen:
    - Binding of antibody can inactivate the antigen (i.e. prevent a virus from binding to cells)
    - Binding of antibody can induce phagocytosis of a particle by macrophages and neutrophils
    - The presence of antibodies on the surface of a cell can activate the complement system to form holes in the cell membrane and lyse the cell

- Antibodies (remember they are just proteins in the blood!) are produced by B cells - there are millions of different types of B cells, and they each code for one specific antibody protein
    - The way this works is that the B cells each have a different genome, meaning that they will each code for a different kind of protein
    - The reason they have a different genome is because as they are made from stem cells in the bone marrow, DNA recombination happens and so each B cell has a slightly different genome and thus makes a different antibody
    - When an antigen matching the B cells comes along, it binds to an antibody molecule on the B cell surface and this tells the B cell to proliferate and differentiate
    - It differentiates into 2 different kinds of cells: plasma cells and memory cells
        - Plasma cells get to work right away, making antibodies for this antigen that originally bound to the B cell and releasing them into the blood
        - Memory cells don't release anything but they hang around, dormant, waiting to see that antigen again
    - This way of selecting B cells to mature (because not all of them are going to bind to an antigen, meaning that not all of them will proliferate!) is called "clonal selection"

- The first time this whole process works, it is called the "primary immune response" - it is not fast enough to prevent symptoms of the infection from occurring because it takes time for the B cells to proliferate and then produce antibodies

- But the next time the immune system sees this bacteria, the "secondary immune response" happens which is because there are already tons of memory cells ready to go

Cell-mediated Immunity and the T Cell

- So there are 2 kinds of T cells: T helpers (aka "CD4 cells") and T killers (cytotoxic T cells, aka "CD8 cells")
    - T helper cells activate B cells, T killer cells, and other cells of the immune system - so they don't really do anything themselves but are of course crucial to the immune response
        - It communicates with other cells by releasing special hormones called lymphokines and interleukins
        - Note that it is the host of the HIV virus -- i.e. this is where HIV attacks
    - T killer cells destroy abnormal host cells (i.e. virus-infected host cells, cancer cells, foreign cells i.e. skin graft, etc.)

- T cells are made in the thymus gland (hence "T"), and the idea is that during childhood, TRILLIONS of different T cells are produced (different as in specific for different antigens)
    - As we progress through childhood, the thymus gland removes the T cells which recognize antigens from our OWN cells (failure to do so will cause an auto-immune reaction, which we don't want)
    - And then for each of the other T cells, when they sense an antigen they will proliferate (as the B cells do) and then it's good times

- The recognition mechanism for T cells works generally through recognizing certain proteins on the cell surface of some suspect cell
- One important group of cell-surface proteins is the major histocompatibility complex (MHC), of which there are 2 types: class I and class II
    - MHC Class I proteins take random samples of peptide from inside the cell and display it on the surface
        - This allows T cells to monitor the internal contents of a cell by just looking at the membrane surface - very useful when the cell is virus-infected and so the virus is displayed on the cell surface
        - Thus MHC Class I proteins are found on EVERY CELL of the body
    - MHC Class II proteins are used to display fragments of cells which have already been recognized as bad and chopped up by macrophages or B cells
        - Only macrophages and B cells do this -- thus they are known as "antigen-presenting cells"
        - So the difference between Class I and II is that the peptide presented in Class I may not be bad, whereas in Class II it is always bad and in fact has already been recognized as such
        - Anyways, the reaction chain for MHC Class II is that the T helper cell will recognize it, then activate B cells and stimulate proliferation of T killer cells, then once all that stuff is built up then the infection will DIE

Other Tissues Involved in the Immune Response

- The tonsils are masses of lymphatic tissue in the back of the throat that "catch" pathogens which enter the body through respiration or ingestion
    - The appendix does the same thing but is located around the large intestine
- Neither of these two guys is essential for

Chapter 7

Chapter 7: Digestive and Excretory Systems

Part 1: The Digestive System

Overview of the GI Tract

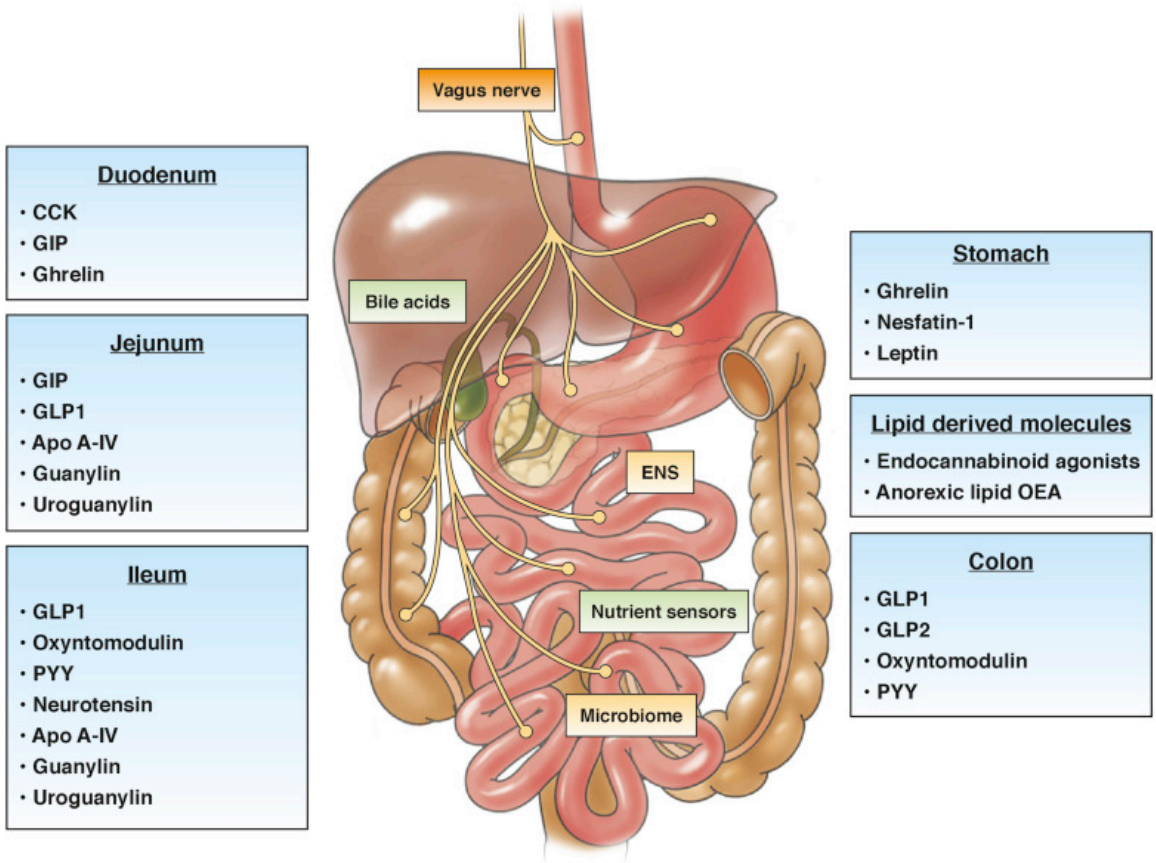
- The basic idea of digestion is that we break down food into its most basic parts by enzymes (hence the term "enzymatic hydrolysis")
- Here are the different foods types and their associated hydrolytic enzymes:
    - 1 triglyceride ----pancreatic lipase----> 2 fatty acids + 1 monoglyceride
    - Polysaccharide ----ptyalin (aka salivary amylase) and pancreatic lipase----> disaccharides
    - Disaccharides ----brush border disaccharidases---> monosaccharides
    - Polypeptide ----gastric acidity/pepsin, pancreatic proteases (trypsin and chymotrypsin)----> dipeptides and tripeptides
    - Dipeptides and tripeptides ----brush border peptidases----> amino acids

- We call the cells lining the GI lumen "epithelial cells" (as opposed to endothelial, or anything else) because epithelial cells are those which line the outside of the body (i.e. skin cells)…and the GI tract is considered to be open to the outside world
- The different sides of an epithelial cell are apical (faces inside the lumen) and basolateral (the sides and "bottom" of the cell)
    - There are tight junctions between apical cells so that nothing can get between those cells unless it is supposed to

- The GI tract has its own nervous system (means that it can do signal integration for some things instead of having to go all the way back to the CNS), and so GI tract motility is controlled by nerves but also by hormones
    - The parasympathetic nervous system stimulates motility and relaxes sphincters
    - The sympathetic nervous system does the opposite

- There are two kinds of secretion: endocrine and exocrine
    - Endocrine excretions release their products into the bloodstream (so think hormones)
        - For example: pancreas
    - Exocrine excretions USUALLY release their products into ducts which eventually bring them somewhere (in this case, into the GI lumen)
        - For example: liver, gallbladder, and pancreas (yes you can be both exocrine and endocrine)
            - Also, some cells in the walls of the gut itself secrete things (i.e. goblet cells secrete mucus)
        - Exocrine glands are composed of specialized epithelial cells which are further organized into sacs called "acini"

The Gastrointestinal Tract

- 

    - Mouth -> esophagus -> lower esophageal sphincter (aka cardiac sphincter) -> stomach -> pyloric sphincter -> duodenum -> jejunum -> ileum -> ileocecal valve -> colon -> external anal sphincter

- The mouth does fragmentation, lubrication, and some enzymatic digestion
    - Saliva contains salivary amylase and lysozyme (kills bacteria, thus helps with immunity)
- The pharynx, or throat, contains openings to both the esophagus (eating) and the trachea (breathing)
    - The esophagus has two sphincters (upper esophageal and lower esophageal) which regulate the movement of food
- The stomach does the following: partial digestion of food, regulated release of food into the small intestine, and destruction micro-organisms…the following things help it to do so:
    - Acidity (kills microorganisms, hydrolyzes proteins, converts pepsinogen to pepsin)
    - Pepsin (a gastric enzyme for proteolysis, thus it breaks down food proteins but also activates chymotrypsin and trypsin)
    - Motility (breaks up food particles and also moves them through)
    - Sphincters (the pyloric sphincter stops too much food from going into the duodenum - this depends on acidity and stretching in the duodenum)
        - Cholecystokinin is the main enzyme that does this
    - Gastrin (this is another hormone secreted by "G cells" in the stomach wall - it stimulates acid and pepsin secretion and gastric motility)
        - Gastrin secretion is stimulated by food in the stomach or by parasympathetic stimulation
        - Histamine acts as a co-factor for the stimulation of acid secretion by gastrin (so sometimes we block histamine to keep acidity levels down)

- The small intestine completes digestion as well as most of absorption…here are the key features:
    - Surface area (the small intestine has a large surface area because of its length, folds, villi, and microvilli)
        - Villi are macroscopic projections into the intestine, microvilli are smaller ones
    - Intestinal villus…it has 3 important structures:
        - Capillaries (absorb the breakdown products of carbs and proteins…they become veins and eventually the hepatic portal vein, which takes them to the liver)
        - Lacteals (absorb the breakdown products of dietary fats…become lymphatic vessels which become the thoracic duct and empties into the general bloodstream -- thus bypassing the liver)
        - Peyer's patches (lymphocytes on the villi which help to protect against gut pathogens and toxins)
    - Bile and pancreatic secretions in the duodenum (pancreatic secretions are digestive enzymes and bicarbonate; bile secretions are made from cholesterol and helps to digest fats)
        - Bile is stored in the gallbladder until needed
        - The bile duct and the pancreatic duct merge at the sphincter of Oddi and so they ultimately both arrive into the GI lumen from the same opening
    - Duodenal enzymes (besides the ones from the pancreas):
        - Cells in the wall of the duodenum secrete stuff to activate pancreatic enzymes (i.e. enterokinase activates trypsinogen)
        - Some enzymes of the duodenum wall do their work AT the wall - they don't go into the lumen (i.e. the brush border disaccharidases)
    - Duodenal hormones:
        - Cholescystokinin (CCK): secreted in response to fats in the duodenum; causes the pancreas to secrete digestive enzymes; stimulates gallbladder contraction; decreases gastric motility
        - Secretin: released in response to acid in the duodenum; causes pancreas to release bicarbonate as a buffer which will neutralize HCl (this is because duodenal pH needs to be kept neutral or even slightly basic for the pancreatic enzymes to function)
        - Enterogastrone: decreases stomach emptying
    - Jejunum and ileum: these are the later parts of the small intestine…they absorb the stuff that the duodenum did not absorb
- The role of the colon (aka large intestine) is to absorb water and minerals, and to form and store feces until defecation
    - Overall, it goes from the cecum to the rectum
        - The appendix is also here - it has a lymphatic function
    - The anal sphincter is made up of internal smooth muscle (autonomic control) and external skeletal muscle (volntary control)
    - The colon contains lots of bacteria which metabolize undigested material (gas is a frequent by-product of this)
        - Colonic bacteria are important because they keep dangerous bacteria from proliferating (because they will compete with them for space and nutrients) and because they supply Vitamin K, for blood clotting

The GI Accessory Organs

- The GI accessory organs are the pancreas, liver, and gallbladder

- Exocrine pancreas releases: pancreatic amylase, pancreatic lipase, nucleases (for DNA/RNA), pancreatic protease
    - It also releases zymogens: trypsin, chymotrypsin, procarboxypeptidase, procollagenase

- The pancreatic secretions are controlled by the hormones CCK and secretin

- Endocrine pancreas is also within the pancreas - it is small regions called the islets of Langerhans
  - There are 3 kinds of cells in these "islets", and they each secrete a unique hormone:
    - Alpha cells release glucagon
    - Beta cells release insulin
    - Delta cells release somatostatin (this inhibits digestive processes)

- So the pancreas has a huge role in maintaining blood glucose
  - Lowering blood glucose: insulin causes the removal of sugar from the bloodstream to be stored in cells…this is important not only so that the cells can get their energy, but also because excess glucose cause neuronal and renal damage
  - Raising blood glucose: glucagon, epinephrine (adrenal cortex), and cortisol (adrenal cortex) all raise blood glucose
    - Low blood glucose is fatal because cells will die, so the role of these 3 guys is very important (whereas insulin not so much because elevated blood glucose isn't that bad…)

- The liver secretes bile, and the gallbladder stores bile
  - Bile is made up of bile acids, which are also called bile salts when they are deprotonated
    - A gallstone is a large crystal formed from bile but with ingredients in the wrong proportions
  - The liver's role is more in processing the food, not with digesting them…
    - It stores sugar as glycogen, makes proteins from amino acids, deals with toxins, etc.
    - It produces most of the blood proteins that circulate in the plasma

A Day in the Life of Food

- Carbohydrates
  - Blah blah blah…OK now we have monosaccharides…we take them into the intestinal epithelial cell by active transport (more specifically a symport, which takes in sugar while allowing sodium to flow in down its concentration gradient as well)
    - This gradient is created by Na/K ATP-ases which take Na out of the cell and into the interstitium (not the GI lumen)
  - Once the concentration in the epithelial cell is high enough, a gradient exists which will allow their facilitated diffusion (uniport) into the capillaries
  - The increased blood sugar levels cause the Beta cells of the pancreatic islets of Langerhans to secrete insulin, which means that not only the liver but also other cells of the body will take up, utilize, and store glucose
- Proteins
  - Blah blah blah…OK now we have dipeptides and tripeptides
  - The brush border peptidases break them down into peptides
  - They get absorbed into the epithelial cells the same as monosaccharides (symport with sodium), and then facilitated diffusion uniport into the capillaries
- Fats
  - Blah blah blah…OK now we have monoglycerides and fatty acids…they diffuse into the epithelial cells by themselves (since they are small and hydrophobic!)
  - Once they get into the epithelial cells, we convert them back to triglycerides and package them in chylomicrons
  - The chylomicrons enter the lacteals and eventually go into the main bloodstream
  - As they bypass cells, the cells take up the fat

- In particular, adipocytes and liver cells have lipoprotein lipase, which hydrolyzes the triglycerides back into monoglycerides and fatty acids, which diffuse into the cells and do stuff

Part 2: The Excretory System

Overview

- The kidneys mainly do excretion…but the liver, large intestine, and skin are all involved as well!

- Liver
  - The liver handles many wastes by modifying them and releasing them into bile, which eventually gets excreted (although, yes, most bile is recycled) -- especially it does this for large OR hydrophobic waste products
  - The liver also makes urea and releases it into the bloodstream to be filtered out at the kidney (the urea comes from nitrogen which comes from protein breakdown)
- Colon
  - The colon doesn't really excrete anything, but it MODIFIES the excrement by reabsorbing water and ions etc. from the stuff that is passing through the GI tract
- Skin
  - Skin produces sweat, which is similar to urine in that it contains water, urea, and ions -- thus skin is in a way, excretory
    - However, it is not PRIMARILY excretory because the main function of sweating is temperature control, not excretion issues…

- Kidneys
  - The kidney has 3 main parts to its operation:
    - Filtration (fluids and small molecules leave the blood and enter the tubules of the kidney)
    - Selective reabsorption (some of the filtrate goes back into the blood)
    - Concentration and dilution (decide whether to take out even more liquid to make the urine concentrated, or to leave it in there)
  - See table:

Anatomy of the Excretory System

- Blood goes into the kidney from a renal artery, and leaves the kidney via the renal vein
- The ureter takes urine from the kidney to the urinary bladder
  - The bladder works like the anal sphincter does - internal layer of smooth muscle, external layer of skeletal muscle
- The kidney has an outer region (cortex) and inner region (medulla)
  - The medulla is organized into "medullary pyramids", which empty at the tip ("papilla") into a space called the calyx
  - The calyces converge to form the renal pelvis, which empties into the ureter
- The functional unit of the kidney is the nephron, which is essentially a renal tubule which receives filtrate at one end and empties into a collecting duct at the other end (which would be the papilla, if we go macroscopic)
  - In more detail, here is the path of blood/filtrate:
    - Afferent arteriole -> glomerulus (ball of capillaries) -> efferent arteriole

        - Pressure differences between the glomerulus and the closely associated "Bowman's Capsule", which is a part of the renal tubule, cause fluid to leak out from the blood into the capsule (although of course, substances which are too big to diffuse such as proteins will stay in the blood)
    - In more detail, here is selective reabsorption:
        - Some of the filtrate in the tubule is stuff that we DON'T want to lose, so it diffuses BACK from the renal tubule to peritubular capillaries, which become venules and then veins and then the renal vein
            - This mostly happens in the "proximal convoluted tubule" (PCT), which is close to the Bowman's capsule
        - All solute movement is accompanied by water movement, which means that the PCT is where most reabsorption of water takes place…the concentration of urine is determined later, by relatively finer-tuned changes
        - Selective reabsorption is selective in that it only reabsorbs certain substances, but it is NOT selective when it comes to how MUCH is reabsorbed - it absorbs all the solute it can (again, solute concentration issues are dealt with LATER on in the tubule)
    - Concentration and dilution
        - The last part of the tubule (distal tubule) takes care of this - the determination of how concentrated the urine is going to be (basically how much water and salt do we keep in the urine)
        - Everything is controlled by two hormones: ADH and aldosterone
            - ADH is anti-diuretic hormone, which means that it prevents diuresis (water loss in urine)…thus when ADH is active, we are going to have a lot of reabsorption of water in the distal tubule meaning that the urine is going to be highly concentrated
                - ADH is a dehydration thing, meaning that dehydration is one of the primary things which sets it off
            - Aldosterone causes Na+ to be reabsorbed more by the nephron, causing the plasma to have higher osmolarity, which will make the person thirsty and also increase water retention…this will increase blood volume which increases blood pressure
                - Aldosterone is a blood pressure thing, meaning that low blood pressure is one of the main things that sets it off

    - Bowman's capsule -> proximal convoluted tubule -> descending limb of the loop of Henle -> ascending limb of the loop of Henle -> distal convoluted tubule -> collecting duct

- The loop of Henle is a "countercurrent multiplier", which basically means that the limbs of the loop of Henle have different permeabilities and go in opposite directions
    - The descending limb is permeable to water, so lots of water leaves and the filtrate becomes very salty
        - The osmotic gradient allowing this is maintained by the fact that the vasa recta (extensions of the efferent arterioles) run around the loop of Henle and take up this water that has been excreted
    - Then in the ascending limb, all that solute leaves because it is permeable to solute but not to water…so the urine is very concentrated at this point
    - Now all the solute is in the medullary interstitium, and it can serve as a gradient to take water out of the filtrate in the collecting duct provided that the correct transporters are in place due to the ADH/aldosterone

- Renal regulation of pH
    - The kidney controls pH by excreting HCO3- when it is too basic, and H+ when it is too acidic
    - The enzyme "carbonic anhydrase" handles this by converting CO2 -> H2CO3 -> H + HCO3, at which point the kidney can excrete either the H+ or the HCO3-
        - Carbonic anhydrase is found in all the nephron's epithelial cells, except for the ones in the thin part of the loop of Henle (which are metabolically inactive)

Endocrine Role of the Kidney

- Know the endocrines for kidney

Chapter 8

Chapter 8 - Muscle and Skeletal Systems

Muscle

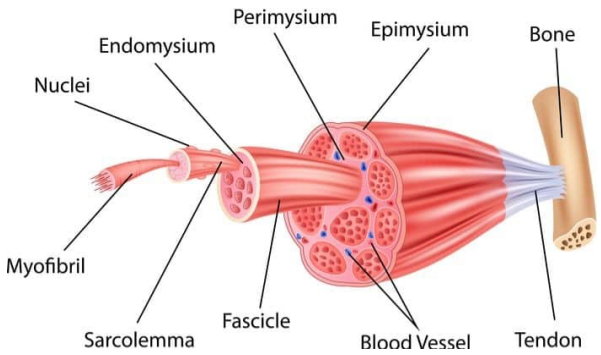
- Types of muscle:
    - Striated
        - Cardiac (involuntary control)
        - Skeletal (voluntary control)
    - Smooth (in the walls of hollow organs i.e. GI tract, urinary system, etc.) (involuntary control)

Skeletal Muscle

- Muscles work by manipulating the skeleton of the body - thus to be effective, they must be attached to bones
    - They are attached at either end of the muscle to bones, via tendons made of collagen
    - They contract (muscles can **never** expand) to provide different kinds of movement:
        - Flex (reduce angle of the joint)
        - Extend (increase angle of the joint)
        - Abduct (move away from the body)
        - Adduct (move toward the body)
- One of the two bones joined by a skeletal muscle is closer to the body, and stays in place when the muscle contracts…so it is the other bone that is moving closer or farther away
    - The point on the non-moving bone where the muscle attaches is called the "origin"
    - The point on the moving bone is called the "insertion"
- Oftentimes, muscles are paired or grouped in order to either coordinate the same movement (synergistic) or the opposite movements (antagonistic, i.e. bicep vs. tricep)

- Structure/physiology of skeletal muscle
    - Muscle tissue is broken down into connective tissue and contractile tissue
        - The contractile tissue is held together in bundles called fascicles
    - Within each fascicle there are fine muscle fibers, called myofibers…which are each actually just one huge cell
        - These muscle cells/muscle fibers are syncytia, meaning that they are the product of many cells fused together (which means that they are often multi-nucleate)
    - Each muscle cell/fiber has a specialized cell membrane called the sarcolemma, which is the normal plasma membrane + polysaccharide and collagen (this allows it to fuse with tendon fibers)
    - Within each muscle cell/fiber there are smaller units called myofibrils, and it is these which provide the force of contraction for the muscle
    - Within each myofibril there are sarcomeres laid down end to end
        - Each sarcomere consists of an overlapping arrangement of polymerized actin filaments (called thin filaments) and myosin filaments (called thick filaments)

Structure of Skeletal Muscle



- Sliding Filament Model of Muscle Contraction
    - The basic idea is that within each sarcomere of each myofibril of each myofiber of each fascicle of each muscle…the thin and thick filaments slide across each other so that they overlap even more…
        - This causes each sarcomere of each myofibril of each myofiber of each fascicle of each muscle…to SHORTEN! Hence muscle contraction!
    - This "filament sliding" is powered by the enzyme "myosin", which uses ATP hydrolysis (note that of course this is a different myosin than the filament which makes up the thick filaments!)
    - The entire sliding process is called a contractile cycle:
        - The myosin "head" binds to a "myosin binding site" on the actin filament (the tail is already bound to the myosin filament)…this is also called "cross bridge formation"
            - At this point it is also bound to ADP and Pi, from a previous contraction (you will see why)
        - The "power stroke" occurs, where the myosin head pulls the actin chain past itself (i.e. the angle between the head and the tail decreases)
            - Here the ADP gets released so that we can...
        - Bind a NEW ATP molecule to the myosin, which causes it to let go of the actin
        - ATP gets hydrolyzed and the myosin head gets cocked back and bound to a new binding site again

- Excitation-Contraction Coupling (basically, a way to control the automatic reaction which would otherwise occur whenever we had actin, myosin, and ATP all in the same environment)
    - The idea is that the "troponin-tropomyosin" complex prevents contraction when Ca2+ is not present
    - Basically, tropomyosin is a long fibrous protein which winds around the thin (actin) filament, blocking all the binding sites…this means that myosin cannot bind!
    - But troponin is a globular protein associated with tropomyosin that, when bound to Ca2+, undergoes a conformational change which will move tropomyosin out of the way, so that the actin filaments can bind
    - So basically…everything is controlled by cytoplasmic Ca2+ levels!

- The Neuromuscular Junction and Impulse Transmission

    - OK the idea is that the neuromuscular junction is the synapse between the axon terminal and the myofiber (muscle cell) - this is where a neuronal signal would cause the cell to do stuff
        - The interesting thing however is that unlike normal synaptic clefts where it is only a certain point, the neuromuscular junction is like a long trough/invagination of the muscle cell - this is so that a signal neuronal signal can depolarize a large region of the muscle cell at once!
            - The neurotransmitter is acetylcholine
            - The "long trough" is called the motor end plate
    - The rest is easy…Ach causes Na influx, which depolarizes the post-synaptic membrane ("end plate potential"), which opens up more voltage-gated sodium channels (if it is big enough) and causes an action potential
        - One cool thing: since action potentials are basically a cell-surface sort of deal, the interior of the myofiber (muscle cell) won't really feel it…so we use transverse tubules (t-tubules) to allow the action potential to reach the interior of the cell
        - Then once the action potential arrives in the interior courtesy of the t-tubules, the sarcoplasmic reticulum does its thing
            - The SR is a huge smooth endoplasmic reticulum which completely surrounds each myofibril…it stores Ca2+, so when it gets that AP, it lets out the calcium which then allows the muscle to contract

- Mechanics of Contraction (i.e. different ways to vary contraction strength)
    - Start with the smallest possible muscle contraction: it is the "twitch", which is when only one motor neuron goes off, and so only the myofibers which are connected to it contract
    - Force of contraction can be increased by:
        - Recruiting motor units: setting off more motor neurons, so that all of their associated myofibers go off as well
        - Frequency summation: so that the Ca2+ never gets fully sequestered by the SR

- Energy Storage in the Myofiber…a few quick shots:
    - The compound creatine phosphate is an "intermediate-term" energy storage molecule that reforms ATP from ADP + Pi
    - Myoglobin delivers the oxygen to the muscle (necessary for cellular respiration to produce more ATP) by taking O2 from hemoglobin as hemoglobin travels through the bloodstream with oxygen attached

- Keener fact:
    - The length of a muscle (i.e. when uncontracted, how much overlap there is between the thin and thick filaments) affects contraction strength - too much overlap and the filaments will interfere with each other, too little overlap and not enough crossbridges can be formed for a powerful contraction
        - This is called the "length-tension" relationship

Cardiac Muscle Compared to Skeletal Muscle

- Similarities:
    - Sarcomeres (thus cardiac muscle is striated because of the "stripes", just like skeletal muscle)
    - T-tubules
    - Troponin-tropomyosin

    - Length-tension relationship (even more significant here because unlike skeletal muscle, where the bones pretty much ensure that the length stays the same, the heart can expand and contract and the muscles WILL be affected)
- Differences:
    - The muscle cells (myofibers) are not syncytial, meaning that they all only have one nucleus
    - All the muscle cells are interconnected by gap junctions called "intercalated disks", which allow action potentials to go through the whole heart (so functionally it is like a syncytium because all the cells are on some level "connected")
    - Motor neurons do NOT determine the contraction of the heart muscles…it's controlled instead by the pacemaker cells
    - The action potential in cardiac muscle is dependent not only on "fast" sodium channels, but also sodium-calcium channels, which are SLOWER to respond…that is why the action potential graph looks like this:

    - Reasons for the "plateau phase":
        - Longer contraction duration: which allows for complete ventricular emptying
        - Longer refractory period: prevents summation and tetanus (would be deadly in the heart)

Smooth Muscle Compared to Skeletal Muscle

- Similarities:
    - Contractile cycle
    - Role of Ca2+
- Differences:
    - It has "functional syncytia" instead of "real" syncytia, just like cardiac cells
    - Action potentials are a mix between skeletal and cardiac:
        - Sometimes it is a "spike" like skeletal (although MUCH, MUCH slower)
        - Sometimes it has a "plateau" like cardiac muscle for prolonged contractions
    - There are no sarcomeres - the thin and thick filaments are instead just hanging around in the cytoplasm (hence the smooth rather than striated appearance)
    - Narrower and shorter than skeletal muscle cells
        - No t-tubules (as mentioned above, they are so small that this is not necessary)
        - Again because of the smaller size, the SR is not necessary because calcium can just come through the membrane
    - No troponin-tropomyosin…instead we use calmodulin and myosin light-chain kinase
    - The neurons which induce contraction are not somatic (as they are with muscle) but instead are autonomic

<u>The Skeletal System</u>

- The vertebrate skeletal system plays 5 roles:
    - Support the body
    - Provide a framework for movement
    - Protect vital organs
    - Store calcium
    - Synthesize elements of blood i.e. red/white blood cells and platelets (this is called hematopoiesis)
- The vertebrate endoskeleton is divided into:
    - Axial components (skull, vertebral column, ribcage)

- Appendicular components (everything else)

Connective Tissue

- All types of connective tissue are derived from the fibroblast
  - Fibroblast can turn into adipocytes, chondrocytes (cartilage), and osteocytes (bone)
  - It can secrete FIBROUS material such as collagen (strength/stability) and elastin (elasticity)
- There are two general categories of connective tissue:
  - Loose connective tissue includes adipose tissue and the extracellular matrix
    - The extracellular matrix includes glycosaminoglycans, which are solvated by water…this gives tissues their thickness and firmness
  - Dense connective tissue refers to bones, tendons, and ligaments

Macroscopic Bone Structure

- Two primary bone shapes: flat (ribs, skull, etc.) and long (limbs)
  - Flat bones do hematopoiesis and protect organs
  - Long bones are for support and movement
- More on long bone structure:
  - Main shaft is diaphysis
  - Flared end is epiphysis

- Two types of bone structure: compact or spongy
  - Compact bone is hard and dense
  - Spongy bone is porous
- Most bones are spongy surrounded by a layer of compact bone
- The diaphysis of long bones is a tube composed of compact bone

- Bone marrow: it is non-bony material found in the shafts of long bones and in the pores of spongy bones
  - Red marrow: found in spongy bone within flat bones…it is the site of erythropoiesis
    - Activity is increased by erythropoietin
  - Yellow marrow: found in shafts of long bones…it is inactive

Microscopic Bone Structure
Cartilage
Bone Growth and Remodeling; the Cells of Bone
Ligaments, Tendons, and Joints

[Chapter 8 Addendum]

Microscopic Bone Structure

- Bone is composed of 2 principal ingredients: collagen and hydroxyapatite
  - The deal is that collagen is laid down in an ordered structure
  - And then hydroxyapatite (calcium phosphate crystals) forms around this framework and make the bone strong and inflexible

- Now think about it on a more macro level - the differences between spongy and compact bone
  - Spongy bone is like a sponge in terms of structure - there are just many spikes of bone surrounding marrow-like cavities (called spicules or trabeculae)
  - Compact bone has a specific structure, and the most basic unit of this structure is the osteon

- OK, let's break down the osteon
    - Starting from the center, there is a Haversian canal where there are blood vessels, lymph vessels, and nerves
    - Then there are layers of bone called lamellae surrounding this center like concentric rings
    - There are tiny channels called canaliculi coming out from the hole, going through the lamellae, and ending up in spaces called lacunae
    - There is an osteocyte - mature bone cell - in each lacunae and so it is through the canaliculi (channels) that the osteocytes can contact each other, get nutrients from the blood, etc.

Cartilage

- Cartilage is something that is found between bones (i.e. at joints)
- It is strong but flexible, so we see it in places of the body where we need that flexible yet strong support, such as: larynx, trachea, outer ear, etc.
- Cartilage is secreted by chondrocytes

- There are 3 kinds of cartilage:
    - Hyaline: strong and SOMEWHAT flexible
        - Found in larynx, trachea, joints
    - Elastic: more flexible than hyaline cartilage
        - So we see this in the outer ear, epiglottis, etc.
    - Fibrous: very rigid and a good support
        - The intervertebral disks of the spinal column - we don't need much flexibility but we want SUPPORT here

- Cartilage is NOT innervated and it DOES NOT have blood vessels
    - So it gets its nutrition from the surrounding fluid
    - But it still doesn't have a direct supply, which means that cartilage injuries take a long time to heal

Bone Growth and Remodeling; the Cells of Bone

- OK, first remember that long bones (like in our arms and legs) are made up of a diaphysis (the tube) and the epiphysis (the flared ends)

- When we are children, there is an epiphyseal plate between the diaphysis and the epiphysis
    - We produce cartilage here and thus the diaphysis and epiphysis are forced apart, and the bone becomes longer
    - Then the cartilage is replaced by bone, so everything hardens and the length increase is permanent
    - After puberty, androgens/estrogens cause the epiphyseal disk to ossify so that no more growing can occur

- What about when we are adults? Well there is no more growth at the epiphyseal plate, but what we do have is the bone continually being degraded and then remade - this process is called remodeling
    - LAYING DOWN BONE:
        - OK so we have osteoblasts in the bone and they just lay down collagen and hydroxyapatite (we know this)
        - But then at a certain point, it is completely surrounded by all this bone it has laid down
        - At this point it stops laying down the bone and just stays in that space of its own

        - The space is called a lacuna (sound familiar?)
        - And the osteoblast is now called an osteocyte (sound familiar?)
    - DESTROYING BONE:
        - The cells which do this are called osteoclasts - they dissolve the hydroxyapatite calcium phosphate crystals, and the bone just collapses

- Of course there are also consequences regarding hormone activity here
    - The more osteoblasts work, the more hydroxyapatite crystals they dissolve, and thus the more calcium and phosphate is in the bloodstream
    - Thus in order to maintain constant calcium levels and phosphate levels, hormones control osteoblast vs. osteoclast activity as well as control the rate of Ca absorption from the intestine
    - Table:

Ligaments, Tendons, and Joints

- Recall that ligaments and tendons are considered to be dense connective tissue, which means that they are strong and they contain a lot of collagen
    - Bones are the other type of dense connective tissue

- Tendons connect bones to muscle
- Ligaments connect bones to other bones
    - The point of connection is called a JOINT
        - Immovable joints are called synarthroses, and basically this means that the 2 bones are fused together (i.e. skull)
        - Slightly movable joints are called amphiarthroses (i.e. vertebral bones)
        - Freely movable joints are diarthroses (i.e. elbow, knee, etc.)

- Thinking more about joints:
    - They are all lubricated by synovial fluid
    - The surfaces of the 2 bones which contact each other are perfectly smooth because they are lined by hyaline cartilage
        - Recall that cartilage has no direct nutrition/materials supply -- this is why it is easy for them to get inflamed, stiff, etc. (think arthritic knees)

Chapter 9

Chapter 9: Respiratory and Skin Systems

<u>The Respiratory System</u>

Functions

- The basic idea is that organisms need oxygen to do oxidative phosphorylation
    - Single-celled eukaryotes can just get it by diffusion
    - Simple multi-celled eukaryotes can do the same

    - But complex multi-cellular eukaryotes like us need to have a whole respiratory system to do this
- Other things the respiratory system does:
    - pH regulation: remember there is a balance between CO2 <---carbonic anhydrase---> carbonic acid
        - Thus the more CO2 we breathe out, the less acid we have, and so the pH of the blood goes up
            - Hyperventilation: too much breathing; causes the blood to be too basic
            - Hypoventilation: too little breathing; causes the blood to be too acidic
    - Thermoregulation: we lose heat when breathing out
    - Protection from disease and particulate matter: air has to go through barriers before reaching the lungs, where they can do harm

Anatomy of the Respiratory System

- The respiratory tract is the passageway used by gases to enter and exit the lungs:
    - Nose: warm/humidify the air; also filter is with nasal hairs and sticky mucus
    - Nasopharynx: open space behind the nose
    - Pharynx: basically the throat
    - Larynx: at the bottom of the throat…it has 3 functions:
        - Keeps the airway open (made entirely of cartilage)
        - Has the epiglottis, which can seal the trachea while swallowing so that food is not "breathed" in
        - Contains the vocal cords, which vibrate when air is passed by them to create sound
    - Trachea: a passageway that must remain open (again cartilage prevent its collapse)
    - Bronchi: branches of the trachea (only 2) (again cartilage prevents their collapse)
    - Bronchioles: branches of the bronchi (NO cartilage)
        - Their walls are made of smooth muscle, so these are the guys which get expanded and contracted to control air flow into the system
    - Alveolar Ducts: ?
    - Alveoli: tiny sacs (one cell large) at the end of bronchioles
        - They have thin walls which allow them to exchange oxygen with the blood

- Role of the respiratory epithelium in protecting against disease and foreign objects
    - Basically until we get to the alveoli, the cells which line the walls of the respiratory tract are epithelial cells, which are too thick to do gas exchange (because they are thick and COLUMNAR) - so air just gets passed (or CONDUCTED) through these areas
    - Some of the epithelial cells (called goblet cells) secrete a layer of sticky mucus
    - Other epithelial cells have cilia which sweep this layer of mucus up towards the pharynx
    - At the pharynx, the mucus traps the pathogens and inhaled particles and can either cough it out or swallow them

- But the actual air exchange takes place in the alveoli, alveolar ducts, and the very smallest bronchi (called respiratory bronchioles)
    - This is called the "respiratory zone" and the epithelium just consists of a single layer of squamous ("flat") epithelial cells called the simple squamous epithlium
    - Protection here is different because we can't have mucus here or else it would stop the diffusion, so instead we use "alveoli macrophages"

- This is stuff secreted by "Type 2 alveolar lining cells" ("Type 1" is the squamous epithelial layer) and it reduces surface tension on the alveoli so that they don't collapse (the water molecules on the surface of the alveoli would clump together and "shrink" the whole thing)

Pulmonary Ventilation

- We get air in and out of the lungs by doing:
    - Inspiration (contract the diaphragm to enlarge the lungs and the chest cavity, which will draw air in)
        - The diaphragm is under the lungs and is normally shaped like a dome, but it flattens when contracted so that the chest cavity + lungs are drawn downward
        - The intercostal muscles (between the ribs) also contract during inspiration, which pulls the ribs upward and further expands the chest cavity
    - Expiration (the lungs spontaneously will recoil and push stuff out - no muscular work needed)
        - But sometimes the abdominal muscles can get in on the act if they contract, because this will press upward on the diaphragm which will shrink the size of the lungs even more and push the air out

- The lungs are elastic bags that if not for the help of other parts of the body, would collapse in on themselves
    - The reason why they don't is because of the "pleural space" - which is between the visceral pleural membrane (lines the lungs) and the parietal pleural membrane (lines the inside of the chest cavity)
    - The two pleural membranes are drawn together because:
        - Surface tension on the water molecules lining the membrane
        - MORE IMPORTANTLY: there is a negative pressure in there, so the membranes are "sucked" together
    - This "sucking attachment" between the two layers is the same reason why when the chest cavity expands, the lungs expand with it (when the chest expands, the pleural pressure decreases even more and so the lungs expand too)

Gas Exchange

- The idea for the pulmonary circulation is that the blood needs to have some way of coming from the heart (deoxygenated), passing through the lungs, then going back to the heart (now oxygenated) so that it can be pumped to the rest of the body where oxygen is needed
- This whole arrangement is called the "pulmonary circulation"
    - Pulmonary artery comes from the heart
    - Artery branches into pulmonary capillaries aka alveolar capillaries
    - A few capillaries go to EACH alveolus and get the oxygen via diffusion (while giving "back" CO_2 of course)
        - These gases diffuse through the "respiratory membrane", which is the combination of the alveolar epithelium + interstitial liquid + capillary endothelium
    - Then the capillaries become venules
    - The venules eventually become the pulmonary vein, which takes everything back to the heart

- Random fact: pulmonary edema is when there is fluid in the lungs resulting from increased blood pressure
    - The idea is that increased blood pressure will expand the alveolar capillaries beyond that which they can naturally dilate, so fluid will come out into the lungs and the alveoli
    - Normally, we fix this by having the lymphatic system carry interstitial fluid out of the lungs

- The exchange of gases is all a result of "partial pressures"…the idea is that anytime you have a collection of gases, they will collectively create a total gas pressure

- Each gas' individual contribution to that pressure is proportional to its abundance within the mixture (i.e. total gas pressure 100 torr, O2 makes up 20% of the gas…partial pressure of O2 will be 20 torr)
- And of course…gas wants to go from a place of higher pressure to lower pressure
- So when we breathe air in and it goes into our alveoli, the O2 is going to diffuse into the alveolar capillaries' blood until the partial pressure between the two places is the same (and CO2 going the other way, of course…)

Regulation of Respiration

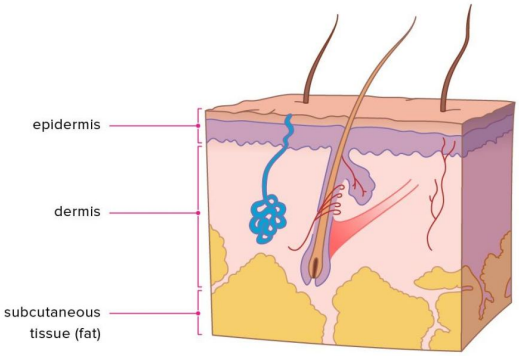
- The big boss here is the "respiratory control center", which is in the medulla of the brain stem…it responds to stimuli by adjusting the rate and depth of breathing
- See table:

- Other interesting points: the walls of bronchi and the larger bronchioles contain smooth muscle, which can contract to close off the bronchi
  - This is good when they are contracting so as to block irritants from going further
  - But it can also be bad when allergy attacks cause the mast cells here to release histamine, which causes bronchoconstriction and stops breathing
    - We deal with this by administering epinephrine/anti-histamines, which will cause bronchodilation

<u>The Skin</u>

Structure

- It is the largest organ in the body (by size and weight)
- It protects us from pathogens and excessive water evaporation, and it regulates body temperature
- It has 3 layers:
  - Epidermis (outermost)
  - Dermis (in the middle)
  - Hypodermis/subcutaneous tissue (inner most; it is essentially an insulating layer of fat)



- The epidermis is basically layers upon layers of epithelial cells (called stratified squamous epithelial cells) - these guys are always reproducing - the top layers get sloughed off and they are replaced by layers at the bottom (called the stratum basale)
    - The cells are also "keratinized", which means that they are surrounded by the protein keratin, which will make them waterproof since it is hydrophobic
    - The cells also have "melanin", which absorbs the UV light from the sun so that the underlying tissues don't get damaged

- The dermis has…
    - Blood vessels (both for the dermis and also the epidermis)
    - Sensory receptors
    - Sweat/oil glands, hair follicles

Temperature Regulation by the Skin

- There are basically 4 ways to cope with cold weather:
    - Contraction of skeletal muscles: either involuntary (shivering) or voluntary (jumping up and down)
    - Insulating fat in the skin which conserves the heat we generate through metabolism
    - "Cutaneous vasoconstriction", which is when we constrict the blood vessels in the dermis so that we don't lose heat via conduction from the blood running through there
        - The sympathetic nervous system also causes this - that's why the skin can become cold and pale when someone is frightened
    - Clothing (duh)

- And for RELEASING heat when it is too warm…
    - Sweating: loss of heat by evaporation
    - Conduction: heat loss by conduction (esp. due to dilating the cutaneous blood vessels)

Chapter 10

Chapter 10: Reproductive Systems and Development

<u>The Reproductive Systems</u>

The Male Reproductive System

- When we are talking about OUTSIDE THE BODY, the 2 principal male reproductive structures are the scrotum and the penis
    - The scrotum is basically just a bag of skin containing the male gonads (aka testicles/testes)
        - The testes have 2 roles:
            - Synthesize sperm (i.e. spermatogenesis)
            - Secrete male sex hormones aka androgens into the bloodstream
        - Interesting point: the testes have to be kept at a specific temperature level which is in fact lower than the rest of the body -- this is why it is kept outside the "main" part of the body

- OK let's think about testes anatomy…
    - Within the testes we have seminiferous tubules (this is where sperm is created)
        - Between these tubules we have the testicular interstitium, which is where we have Leydig cells which synthesize androgens (such as testosterone)
    - Anyways, the seminiferous tubules empty into the epididymis, which is a long tube coiled on the back of each testicle

    - From there we go to the vas deferens
        - Sperm goes from the vas deferens into the inguinal canal, where it meets the other vas deferens (from the other testes) to form a common ejaculatory duct (so this is where the sperm waits before ejaculation)
        - Also contributing to the ejaculatory duct are the "accessory glands", which create semen (a nourishing environment for the sperm) which combines with the sperm
            - The glands are:
                - Seminal vesicles: contributes fructose and other stuff
                - Prostate gland: alkaline secretions for neutralizing acidity within the urethra and the vagina
                - Bulbourethral gland: viscous and alkaline secretion (for lubrication and neutraliziation)
    - From there we go to the urethra, which is in the penis (so we are now in the penis)

- Let's talk about erections - the reason why we get erections is because there is erectile tissue in the penis with special veins and capillaries that can take a lot of blood at high pressure, thus becoming stiff
    - This erectile tissue is found in the corpus cavernosum and the corpus spongiosum of the penis

- The 3 stages of the male sexual act are: arousal, orgasm, and resolution
    - Arousal:
        - PARASYMPATHETIC input
        - There are 2 stages here:
            - Erection (dilate and fill the arteries supplying the venous tissue to cause swelling)
            - Lubrication (bulbourethral glands secrete a viscous mucus which serves as lubricant)
    - Orgasm:
        - SYMPATHETIC stimulation/input
        - There are 2 stages:
            - Emission (so this is when the sperm from the vas deferens and the semen from the accessory glands combine in the urethra to prepare to leave)
            - Ejaculation (semen is propelled out of the urethra by rhythmic contractions of muscles surrounding the base of the penis)
                - Note that this is a REFLEX reaction performed whenever there is semen in the urethra
    - Resolution:
        - SYMPATHETIC input
        - This is just the return to a normal, unstimulated state -- so the arteries serving the penis constrict, there is less blood accumulated in the penis, etc.
        - About 2-3 minutes

- Let's talk about semen:
    - Only 2% sperm
    - 60% seminal vesicles output
    - 35% prostate gland output
    - 3% bulbourethral gland output

Spermatogenesis

- Quickly, the basics:

    - So spermatogenesis is basically a male doing meiosis to produce a haploid gamete called spermatozoa (aka sperm)
        - When females do this, the resultant gamete is called "ova", aka egg
    - Fertilization occurs when a sperm, after having been deposited into the female genital tract, swims to meet the egg and enters it, thus producing a zygote
        - Notably then, the only thing the male contributes to the eventual human is the genes - everything else is from the egg (this is why the DNA of the mitochondria is maternally inherited!)

- Sperm synthesis is done in the seminiferous tubules of the testes
    - Sertoli cells are found in the walls of the tubule and so a sperm starts from the outer wall and moves inward towards the lumen
    - By the time it reaches the lumen, meiosis has been completed and it is ready to go, so we deposit it into the lumen and are off to the races

- More on the conversion of spermatids into spermatozoa:
    - So we get the DNA chromosomes condensing, the cytoplasm shrinking, and the cell shape changing so that we have a head (contains nucleus) and a tail (the flagellum)
        - The base of the tail is like a "neck", and there are many mitochondria here which produce energy using fructose so that the flagellum can move
        - More on the head…it contains:
            - Acrosome (contains hydrolytic enzymes for penetration of the ovum's protective layers)
            - Bindin (protein on the sperm's surface that attaches to receptors on the membrane surrounding the ovum)

- Let's talk about the hormones which control spermatogenesis:
    - Testosterone - stimulates the division of spermatogonia
    - Lutenizing hormone (LH) - stimulates the Leydig cells to secrete testosterone
    - Follicle-stimulating hormone (FSH) - stimulates the Sertoli cells
    - Inhibin - inhibits FSH release (for negative feedback reasons)
        - Are you surprised that the Sertoli cells produce this thing?

Development of the Male Reproductive System

- So let's remember - when we are just an embryo, we DO have a sex, but it's just that we have not seen the sex yet in terms of a repro. system that is either distinctively male or female
- Instead, we have "Wolffian ducts" and "Mullerian ducts" at the same time
    - Wolffian ducts can POTENTIALLY turn into male internal genitalia: epididymis, seminal vesicles, and vas deferens
    - Mullerian ducts can POTENTIALLY turn into female internal genitalia: fallopian tubes, uterus, and vagina
- Then the deal is that the "Y" chromosome will determine which of these 2 structures DOES end up developing
    - If there is no "Y", then the Mullerian ducts will develop (along with the external female genitalia) and the Wolffian ducts will take a hike
    - If there IS a "Y", then the Mullerian Inhibiting Factor is secreted to shut down the Mullerian ducts, and instead we get testosterone which encourages the Wolffian development

The Androgens

- Straight-up definition: all hormones involved in the development and maintenance of male characteristics are called "androgens"
    - The primary androgen is of course testosterone
    - But however, it has to be converted to dihydrotestosterone in the cells of target tissues before it has any effect

- Testosterone is produced during development as needed in order to develop the male internal and external genitalia
    - But then after that, it falls to lower levels…until puberty…
    - At puberty, it increases again so that sperm is produced…also so we get the development and maintenance of male secondary sexual characteristics
        - Notably we get voice deepening, epiphysis fusion (bones), etc.

Female Reproductive System: Anatomy and Development

- OK so there is a lot of homologous development here (i.e. similar to males) -- because there are those non-differentiated structures in embryos
    - Instead of testes we have ovaries, which secrete ESTROGENS (the female sex hormones)
    - The LABIOSCROTAL SWELLINGS grow into the scrotum for the male, but into the "labia majora" of the vagina
    - Instead of the penis we get the clitoris
        - Under the clitoris we have the urethral opening, where urine leaves
        - Surrounding this opening we have the labia minora
    - We also have the opening of the vagina between the labia minora

- After this we are getting to the vagina and internal female genitalia where there is NO HOMOLOGY because it develops from the Mullerian ducts, which are DISTINCTLY female
    - We have the vagina, which is basically a tube
    - The uterus opens into the vagina, and this opening is called the cervix
    - The uterus has multiple layers of lining in it:
        - Endometrium - nourishes a developing embryo (or is shed each month to cause menstruation)
        - Myometrium - layer of smooth muscle which makes up the wall of the uterus
    - Coming out of the uterus there are 2 fallopian tubes which end in fimbriae
    - The fimbriae contact the ovary…(so the egg goes from the ovary into the Fallopian tubes…)

- The female sexual act has the same stages as the male one:
    - Arousal:
        - Again PARASYMPATHETIC
        - Again divided into 2:
            - Erection - clitoris and labia minora contain erectile tissue and become engorged with blood
            - Lubrication - provided by mucus secreted by Bartholin's glands and the vaginal epithelium
    - Orgasm
        - Again SYMPATHETIC
        - It also involves muscle contractions (which include the widening of the cervix so that sperm can move into the uterus)
        - However, no ejaculation

- Resolution
    - Again SYMPATHETIC
    - But it takes 20-30 minutes instead of 2-3

Oogenesis and Ovulation

- The first difference is that the "gonia's" are produced when the females are EMBYROS -- as opposed to only when they become teenagers
    - So basically we have large numbers of oogonia being produced when the female is an embryo
    - Some of these become primary oocytes but GO NO FURTHER until puberty for the female
    - Then every month, a few oocytes mature into ova

- Meiosis in females
    - This is different too in that when we get cell division (for both Meiosis I and II) the resulting species are not the same
        - After Meiosis I we get the main egg (has most of the cytoplasm) and the first polar body (half the DNA as required but very little cytoplasm)
        - After Meiosis II -- which just happens to the main egg -- we get the main egg and the second polar body
    - So the result is that meiosis results in only ONE GAMETE, not four
    - Also because of the way that only a few oocytes go at a time for females, most oocytes are stuck in Prophase I for a LONG time…
        - But when it comes their turn to become eggs (remember this happens to just 1 or 2 per month), they re-enter the meiotic cycle and continue on to form the egg which will hopefully be fertilized
            - However many oocytes never get this and so they die

- What actually happens is that the egg does Meiosis I and becomes a secondary oocyte, then it goes into the fallopian tube (i.e it is ovulated) -- but note that Meiosis II has not happened yet so there is still more to go
    - In fact the way it works is that the secondary oocyte only goes on to do Meiosis II if a sperm enters (fertilizes) it
        - When a sperm does enter, the DNA does not fuse until the egg first finishes doing Meiosis II, and then they fuse
    - So if the woman does not have sex that month, then when menstruation occurs, it is not a mature egg cell that is lost but rather a secondary oocyte

- Let's talk about follicle development…
    - The follicle is something that surrounds the primary oocyte
        - So every primary oocyte is surrounded by a follicle - basically the follicle is made up of granulosa cells -- they support and nurture and help with development (the male equivalent is the sertoli cells)
    - The first "phase" of the follicle is the "primordial" follicle
        - Then it becomes a "primary follicle" when the granulosa cells proliferate to form several layers around the oocyte
            - At this stage the oocyte also adds some mucopolysaccharides called the "zona pellucida" (inside the granulosa layer)
            - And there is also the "thecal cells" added (OUTSIDE the granulosa layer)
                - The thecal cells, since they are the "interstititum", are like the Leydig cells in the male -- so unsurprisingly they are BOTH stimulated by LH

- Ultimately only one follicle per month becomes a mature or "Graafian" follicle
    - The Graafian follicle bursts and the secondary oocyte goes into the fallopian tube
        - The oocyte keeps its granulosa cells though and they are now called the corona radiata

The Menstrual Cycle

- Quick introduction for estrogen/progesterone…
    - Both estrogen and progesterone play a role in the menstrual and pregnancy
    - The follicle synthesizes estrogen
    - After ovulation, the remaining follicular cells form the corpus luteum and secrete estrogen and progesterone

- Now to the cycle…there are TWO ways to describe it, and they differ based on which part of the reproductive system we are considering the changes to
    - ENDOMETRIAL CYCLE:
        - 3 stages: proliferative phase, secretory, and menstrual
            - Proliferative: estrogen produced by the follicle induces endometrial proliferation (i.e. it gets thicker and prepares for implantation)
            - Secretory: this happens after ovulation and so the corpus luteum is formed and it secretes estrogen and progesterone to further develop the endometrium
                - Here we see secretion of glycogen, lipids, and other material…
            - Menstrual: so we assume that fertilization does not occur, which means that the corpus luteum decreases, thus estrogen and progesterone do as well, thus the endometrial lining falls off
    - OVARIAN CYCLE:
        - 3 stages: follicular, ovulatory, luteal phases
            - Follicular: so here a primary follicle matures and secretes estrogen
                - The estrogen acts locally to cause that follicle to finish off meiosis I
            - Ovulatory: now the oocyte is a secondary oocyte, and ovulation occurs and it leaves the ovary
                - It travels down the Fallopian tube towards the uterus
            - Luteal: now the ovary doesn't have the egg anymore, but it has the leftover granulosa cells from the follicle which once housed the egg…these cells turn into the corpus luteum and secretes the estrogen and progesterone which starts the secretory phase in the endometrium

- OK let's also talk about pituitary hormones and how they affect this whole process
    - The chief ones are FSH and LH (note that they are stimulated by gonadotropin releasing hormone, released by the hypothalamus)

Hormonal Changes During Pregnancy

- OK, so now we're talking about pregnancy -- what happens to hormones? (note that they have to differ in SOME way from non-pregnant situations because if they didn't, the uterine lining would get sloughed off as usual and the implanted embryo is screwed)
    - It's all about feedback cycles…
        - Pregnancy means constant high levels of estrogen and progesterone

        - Therefore there is negative feedback on the pituitary and we don't have LH release
            - Which means that there is no ovulation
        - But then how do we prevent corpus luteum degeneration from occurring (this is what happens when LH decreases)? We prevent it through the secretion of human chorionic gonadotropin (hCG), which is secreted by the placenta

- The placenta is basically what ends up after the zygote implants itself into the endometrium

<u>Development</u>

Fertilization and Cleavage

- OK let's talk about how fertilization happens
    - First the egg - recall that after it is ovulated, it still has two layers around it: the zona pellucida (just outside the membrane) and the corona radiata (outside the zona pellucida)
    - Then the sperm - if intercourse occurs and it is deposited near the cervix, then it gets capacitated ("activated") and attempts to swim through the uterus towards the secondary oocyte (egg) in the Fallopian tube
    - If we are lucky (or unlucky!), a sperm penetrates the corona radiata and the zona pellucida and then gets into the egg
        - It accomplishes this penetration of the protective layers using the "acrosome reaction", which is when the acrosome in the sperm head releases hydrolytic enzymes
            - Also in this process we see the "acrosomal process" which sticks out of the sperm, going to the vitelline layer (the zona pellucida) and binds to it using "bindin"
    - Once the sperm is inside, the secondary oocyte does meiosis II and we get an ootid + second polar body
    - The ootid becomes an ovum (more mature version)
    - The sperm and egg nuclei fuse and we get our zygote…and we are good to go!

- Now how about when stuff goes wrong? For example POLYSPERMY - when multiple sperm enter the egg
    - We have 2 ways to prevent this…
        - FAST BLOCK: the egg plasma membrane depolarizes, which prevents additional sperm from fusing with the membrane
        - SLOW BLOCK: due to the depolarization, calcium enters the cell and causes the "cortical reaction"
            - The "cortical reaction" means that:
                - The space between the vitelline layer and the plasma membrane swells
                - The vitelline layer hardens
                - The pH in the egg changes, which causes increased metabolism and protein synthesis

- CLEAVAGE: so this is all about how the zygote develops after fertilization
    - It all happens through the process of embryogenesis
        - And the first step of embryogenesis is cleavage - the zygote undergoes many cell divisions and we end up with a ball of cells called the MORULA
        - After the morula we get the blastocyst
            - The blastocyst has an inner and outer cell mass (basically a ball inside a ball)
            - The "inside ball" sticks to the "outside ball" at one end of the cavity

- We end up with the inner cell mass becoming the embryo
- We end up with the outer cell mass becoming the trophoblast, which becomes the chorion (part of the placenta)

Implantation and the Placenta

- OK so the blastocyst gets to the uterus (remember it started in the Fallopian tubes) and implants
    - This takes about ONE WEEK (after fertilization)
- Implantation is facilitated through the secretion of endometrium-lysing proteases released by the trophoblast (outer layer of the blastocyst as you recall)
- And so right now we have the trophoblast between the embryo and the mother's wall -- and so nutrients etc. are exchanged through the trophoblast
- Eventually the placenta forms, which is specialized for this transfer of nutrients
    - This takes about 3 months
        - What is the significance of that? It is that until we get the placenta up and running, we still need the corpus luteum for its estrogen and progesterone producing ability
        - Therefore human chorionic gonadotropin is important -- this is released by the chorion (recall that the trophoblast basically just turns into the chorion)

- It should also be noted that part of placental development is the formation of placental villi -- these are projections from the placenta into the endometrium which allow the exchange of substances from the maternal bloodstream to the infant's
    - Note that the blood itself never gets transferred!

- Now finally let's think about the inner cell mass…what becomes of it?
    - Well it's not only the embryo -- also we get the amnion, yolk sac, and allantois
        - The amnion is a membrane that surrounds a fluid-filled cavity in which the embryo resides (so "water breaking" is when the amnion breaks and all this water comes out)
        - Yolk sac stores yolk for reptiles and birds, but for humans it is the place for RBC synthesis
        - Allantois - it forms the blood vessels for the umbilical cord, which transports blood between the embryo and the placenta

Post-Implantation Development

- OK a few things happen here…gastrulation and then neurulation

- First let's talk about gastrulation:
    - It is basically the development of the embryo into a structure with 3 distinct layers: endoderm, mesoderm, and ectoderm
    - Following is a table describing which body parts come from which layer:

- Then after gastrulation is neuralation -- the formation of the nervous system

        - What we do is we pinch off a layer of ectoderm (remember this is where the nervous system develops from) to form the dorsal neural groove, which becomes the neural tube
            - Other ectodermal cells go to other parts of the body to from the PNS

- Lastly, let's think about development from a macro view
    - We can divide it into embryonic and fetal stage
        - Before 8 weeks we have the embryonic stage
            - Here organogenesis occurs: the development of organ systems
        - After 8 weeks we are considered a "fetus" so it is the fetal stage
            - Organogenesis has completed so now the systems are just growing and maturing

Differentiation

- OK so differentiation is basically the process of cell specialization - they get better at certain abilities and decrease in others
- Primitive cells in an early embryo have the potential to become any cell type, and they are thus called TOTIPOTENT CELLS
    - At some point in their life, the fate of totipotent cells is determined -- so they aren't specialized yet, but we KNOW what they are going to be -- so this is "determination"
        - Determination can be induced by a cell's environment OR it can be pre-programmed
    - Later on they actually differentiate…

- Just to screw things over, there is also "de-differentiation", which is differentiation backwards
    - This can cause cancer!

Birth and Lactation

- Remember that birth is also known as "parturition"
    - Birth in general is dependent on the contractions of muscles in the uterine wall which will push the baby out
        - How can this happen, based on the fact that progesterone usually prevents the uterine from contracting during pregnancy? It's because oxytocin is released by the posterior pituitary and also the estrogen:progesterone ratio changes
    - When the actual contractions begin, we get a positive feedback cycle where the stretch of the cervix causes the uterine contractions to increase in intensity, which makes the cervix stretch more, etc.

- We can divide labor into 3 stages:
    - Dilation of the cervix (way more so than normal)
    - Actual birth: baby goes through the cervix and birth canal
    - Expulsion of the placenta

- OK now let's think about milk secretion
    - Firstly, the breasts get bigger during pregnancy due to the estrogen and progesterone which the placenta releases
        - However they prevent milk from being released
    - After birth, estrogen and progesterone decrease (thus milk is not prevented from being released) and insetad we get prolactin released from the anterior pituitary -- the prolactin cuases milk to be produced
    - When it comes time for the milk to actually be released, the baby suckles the breast which causes oxytocin to be released from the posterior pituitary, which further allows "milk let-down" (i.e. the release of milk)